Supplementary Appendix

Supplement to: Yuen M-F, Lim S-G, Plesniak R, et al. Efficacy and safety of bepirovirsen in chronic hepatitis B infection. N Engl J Med. DOI: 10.1056/NEJMoa2210027

This appendix has been provided by the authors to give readers additional information about the work.

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Contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. M-F Yuen, J Cremer, R Elston, S Kendrick, F Campbell, M Paff and D Theodore contributed to the conception and design of the study. M-F Yuen, S-G Lim, R Plesniak, K Tsuji, C Pojoga, HLA Janssen, A Gadano, C Petru Popescu, G Diaconescu, T Asselah, HJ Yim, E Janczewska, J Heo, A Wong, G Rizzardini, S-J Park, N Idriz, M Imamura, K Takaguchi, P Andreone, J Hou, M Arbune, A Vata and T Stepanova contributed to the acquisition of data. J Cremer, R Elston, T Lukić, G Quinn, L Maynard, S Kendrick, H Plein, F Campbell, M Paff and D Theodore contributed to data analysis and interpretation.

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Data sharing statement

Within 6 months post US and EU regulatory approval and publication of this study, anonymized individual participant data, the annotated case report form, protocol, reporting and analysis plan, dataset specifications, raw dataset, analysis-ready dataset, and clinical study report will be available for research proposals approved by an independent review committee. Proposals should be submitted to either ViVli Center for Global Clinical Research or www.clinicalstudydatarequest.com. A data access agreement will be required.

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Note: 14 sites did not enroll any participants.

Supplementary Methods

Pre-specified study outcomes

Prespecified study outcomes are shown in **Table S1**.

Table S1. Pre-Specified Study Outcomes.

Objectives	Estimand/Endpoints	Reported in article
Primary		
Efficacy: To assess the efficacy of the three dosing regimens of bepirovirsen in participants with CHB	Primary estimands supporting the primary objective are defined as: - **Population**: separate assessment for the following: • Participants with CHB on stable nucleos(t)ide therapy • Participants with CHB not currently on nucleos(t)ide therapy - **Variable**: Participants achieving HBsAg<LLOD and HBV DNA<LLOQ for 24 weeks after the planned end of bepirovirsen treatment in the absence of rescue medication. - **Treatments**: Groups 1, 2, and 3. Estimation of the within-group response rate. - **Intercurrent events**: Use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to bepirovirsen will be handled assuming they had not happened (hypothetical strategy). **Population summary**: Proportion of participants who achieve response for each treatment group.	Yes
Secondary		

Efficacy: To assess the efficacy of bepirovirsen on biomarkers and virus-specific antibody responses	The estimands supporting this secondary objective are defined as follows: - **Population**: Separate assessment for the following: • Participants with CHB on stable nucleos(t)ide therapy • Participants with CHB not currently on nucleos(t)ide therapy. - **Treatments**: Groups 1-4. Estimation within each group. - **Intercurrent events**: Use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication will be ignored (treatment policy strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy) **2) Categorical Variables**: - Achieving HBsAg <LLOQ and HBV DNA <LLOQ at the end of treatment. - Categorical changes from baseline in HBsAg (e.g., <0.5, ≥0.5, ≥1, ≥1.5, ≥3 $\log_{10}$ IU/mL) and in HBV DNA (e.g., <1, ≥1, ≥2, ≥3 log IU/mL) - ALT normalization (ALT≤ULN) over time in absence of rescue medication in participants with baseline ALT>ULN - HBe antibody (anti-HBeAg) levels - **Population summary:** Proportion of participants in each category for each treatment group. **2) Continuous Variables**: Actual values and change from baseline over time of HBsAg and HBV DNA and actual values and change from baseline of HBeAg levels; HBs antibody (anti-HBsAg) levels - **Population summary**: Mean values and mean changes from baseline for each variable in each treatment group **3) Time to Event Variable**: Time to ALT normalization in absence of rescue medication in participants with baseline ALT>ULN - **Population summary**: Turnbull's estimate for non-parametric estimation of time to ALT normalization in each treatment group	Yes

Efficacy: To compare the efficacy between 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks of bepirovirsen treatment	The same definition as the primary estimand except treatments and population summary are defined as: -**Treatments**: Groups 1, 2, and 3. Three treatment comparisons between: Groups 1 & 2, Groups 1 & 3, and Groups 2 & 3 - **Population summary**: Difference between treatment groups in proportion of participants who achieve HBsAg<LLOD and HBV DNA<LLOQ for 24 weeks after the planned end of bepirovirsen treatment in the absence of rescue medication	Yes
Pharmacokinetics (PK): To characterize bepirovirsen and nucleos(t)ide PK in participants with CHB	• In a subset of participants with intensive PK sampling: Derived bepirovirsen and nucleos(t)ide plasma PK parameters including, but not limited to, AUC, $C\tau$, C_{max}, t_{max}. • In all participants: $C\tau$ and $t_{½}$ of bepirovirsen.	Data analyses are being completed and are planned to be submitted for publication separately
Safety		
Safety: To assess the safety and tolerability of bepirovirsen when dosed for 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks duration in participants with CHB	• Clinical assessments including, but not limited to vital signs, laboratory measurements and adverse events	Yes
Exploratory		

PK-PD relationships: To evaluate PK-efficacy relationship and PK-safety relationship	Exploratory graphical analyses will be initially performed for efficacy (e.g., HBsAg) and safety endpoints. If a relationship between exposure and efficacy and/or safety endpoints is present, population PK-PD modeling will be conducted using non-linear mixed effect methods. The model will assess the effect of various factors (covariates) of the modeled efficacy or safety endpoints. Relevant PK-PD model endpoints e.g.,: • Apparent clearance • Apparent volume of distribution • IC_{50} • Random variability	Data analyses are being completed and are planned to be submitted for publication separately. Preliminary results were presented at EASL 2022 (Yuen MF, et al. Abstract LB004A & B).
Efficacy: To compare the efficacy between 12 weeks of bepirovirsen treatment with a loading dose or without a loading dose	The same definition as the primary Estimand except treatments and population summary are defined as: - **Treatments**: Group 3 & 4. Treatment comparison between Groups 3&4. - **Population summary**: Difference between treatment Groups 3 & 4 in proportion of participants who achieve HBsAg<LLOD and HBV DNA<LLOQ for 24 weeks after the planned end of bepirovirsen treatment in the absence of rescue medication	Yes
Efficacy: To assess the PD effect of bepirovirsen on exploratory viral biomarkers	HBV core related antigen (HBcrAg), HBV RNA	Data analyses are being completed and are planned to be submitted for publication separately

Virology: To assess the effect of genotype/phenotype and presence of baseline polymorphisms within the bepirovirsen binding site to assess the effect on treatment response. To assess the emergence of mutations within the GSK binding site, and elsewhere in the hepatitis B genome, during and after treatment.	Sequencing of the viral HBV DNA and/or HBV RNA prior to treatment, during treatment and post treatment visits	Data analyses are being completed and are planned to be submitted for publication separately
Immunology: To assess the effect of 12 weeks, 12 weeks + 12 weeks step-down or 24 weeks treatment with bepirovirsen on immunological biomarkers. To describe the relationship(s) between virology biomarkers, including but not limited to HBsAg, and immunological biomarkers.	Laboratory measurements of and correlation between the following • Virological biomarkers, as determined by (but not limited to) specific viral parameters (HBeAg, HBV DNA, HBV RNA, HBcrAg). • Soluble immunological biomarkers, as determined by (but not limited to) levels of circulating cytokines and chemokines. • Markers of immune cell function, as measured by (but not limited to) relative frequencies of immune cell subsets among PBMCs, activation status as determined by phenotyping and gene expression patterns, and functional assays including HBV-specific cytokine and/or antibody production	Data analyses ongoing and are planned to be submitted for publication separately

Patient-reported Outcomes: To assess changes from baseline in patient-reported outcomes following 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks of treatment with bepirovirsen.	Change from baseline of HRQoL and EQ-5D.	Additional analyses are planned to be conducted and reported separately to allow a more comprehensive/long-term follow-up overview on the health outcomes impact of bepirovirsen (may include other bepirovirsen study results)

ALT, alanine transaminase; AUC, area under the concentration-time curve; CHB, chronic hepatitis B; C_{max}, maximum observed concentration; Cτ, concentration at the end of the dosing interval; EQ-5D, EuroQol-5 Dimensions; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HRQoL, health-related quality of life; IC_{50}, half maximal inhibitory concentration; IP, Investigational Product; LLOD, lowest limit of detection; LLOQ, lowest limit of quantification; PBMC, peripheral blood mononuclear cell; PD, pharmacodynamic; PK, pharmacokinetic; t½, terminal half-life; T_{max}, time of C_{max}; ULN, upper limit of normal.

Sample size determination

Approximately 440 participants were planned to be randomly assigned to study intervention. For each population, approximately 66 participants were planned in each of the first three treatment groups. Approximately 22 participants were planned in the fourth group.

It is assumed that the number of responders follows a Binomial distribution, with a weakly informative prior (Beta (0.5, 0.5)) for the true response rate. The precision for a range of response rates with 95% credible intervals (CrI) are shown in **Table S2**.

Table S2. 95% Credible Interval of Response Rate by Sample Size.

Sample size per group	Number of responders	Response rate	95% credible interval*
22	2	9%	1%–23%
	3	14%	3%–30%
	4	18%	5%–36%
	5	23%	8%–41%
	6	27%	11%–46%
66	6	9%	3%–17%
	9	14%	6%–23%
	12	18%	10%–28%
	15	23%	13%–33%
	18	27%	17%–38%

*95% highest posterior density interval.

The lower bounds of 95% CrI exclude the historical placebo response rate of 3% if observed response rate is greater than or equal to 14% in Groups 1–3 or 18% in Group 4.

The operating characteristics based on at least 75% posterior confidence that the true rate exceeds a threshold of interest, are shown in **Table S3**, for various sample sizes, and true cure rates. The operating characteristics shown are based on a Bayesian model without consideration of baseline stratification factors and expected to be similar to operating characteristics from the hierarchical model.

With a true response rate of 20%, the proposed sample size of n=66 for Groups 1–3 has ~70% probability of confirming a true response of at least 15%, and if the true rate is 30%, there is an 88% chance of confirming a true response of at least 20%.

Table S3. End of Study Operating Characteristics by Sample Size.

Criterion	**Sample size per group**	**Minimum number (%) of responders required to meet criterion**	**Probability of meeting criterion under various assumptions**			
			True response rate=5%	**True response rate=20%**	**True response rate=25%**	**True response rate=30%**
Probability (true response rate >15%) >75%	22	5 (23%)	0%	46%	68%	84%
	44	9 (20%)	0%	53%	81%	91%
	66	**12 (18%)**	**0%**	**69%**	**93%**	**99%**
	88	16 (18%)	0%	71%	95%	100%
Probability (true response rate >20%) >75%	22	6 (27%)	0%	27%	48%	69%
	44	11 (25%)	0%	25%	56%	81%
	66	**16 (24%)**	**0%**	**23%**	**60%**	**88%**
	88	21 (24%)	0%	22%	64%	92%
Probability (true response rate >25%) >75%	22	7 (32%)	0%	13%	30%	51%
	44	13 (30%)	0%	9%	29%	58%
	66	**19 (29%)**	**0%**	**6%**	**28%**	**63%**
	88	25 (28%)	0%	4%	27%	67%

Note: If the true response rate is 0%, the probability of meeting each criterion is 0% for all sample sizes.

There were no plans for sample size re-estimation.

Analysis of study outcomes

Two approaches were used to handle missing hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA data. If wide disruptive events (such as the COVID-19 pandemic) prevented assessment of the primary outcome, the missing values were handled implicitly by the Bayesian model under the assumption of missing at random. For other missing data (e.g., participant withdrawal from the study), the participant was assumed not to have achieved the primary outcome (non-responder imputation).

Summary data related to the primary outcome use the intent-to-treat (ITT) population N number as denominator for percentages rather than the number of participants with available data at the specific time point of interest. Analysis of difference between treatment groups in the proportion of participants achieving the primary outcome, point estimates of differences in response rate with 95% CrI were calculated for each treatment comparison by calculating differences between the posterior distributions obtained from the Bayesian hierarchical model for the primary endpoint in each group. Samples from the posterior distribution of the response rates in each group were used to obtain posterior probabilities of interest (e.g., Pr(Group 1 – Group 2 > -5% | Data)). The point estimates of differences in response rate with 95% CrI were calculated for each of the treatment comparisons.

Turnbull's non-parametric estimator was used to estimate time to alanine aminotransferase (ALT) normalization in the absence of newly initiated antiviral treatment in participants with baseline ALT >upper limit of normal (ULN). ALT normalization was defined as a return to ≤ULN (ULN = 40 IU/L for males and 33 IU/L for females) in participants with ALT >ULN at baseline. Time to ALT normalization was defined as time from baseline to the first follow-up where participant's ALT has returned to normal. For participants who withdrew from the study or those with ALT >ULN at the end of study, time to ALT normalization was censored at the time of last visit with non-missing ALT value available. Participants who received newly initiated antiviral treatment were censored at the end of the follow-up period. The estimand supporting this secondary endpoint for each population is Turnbull's estimator for the non-parametric estimation of time to ALT normalization treatment in the absence of newly initiated antiviral treatment in each treatment group regardless of completing treatment, interruptions in treatment or adherence to treatment in the absence of newly initiated antiviral treatment. **Intercurrent events**: use of medication for the purpose of suppressing HBV replication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to treatment will be ignored (treatment policy).

A Receiver Operating Characteristic (ROC) analysis explored the relationship between the true positive rate (sensitivity) and false positive rate (1-specificity) for a range of baseline HBsAg cut-offs as a predictor of response. The optimal cut-off was determined by considering the baseline HBsAg cut-point that would maximize the sensitivity, or the proportion of the population who would be responders, and minimize the enrollment of participants who would be unlikely to be responders based on baseline HBsAg for future studies, while also considering practical application.

Primary analyses

All analyses were conducted separately for the two populations (receiving NA therapy and not receiving NA therapy). The participant population was not included as a stratification factor in the analysis model.

The primary assessments of interest are the point estimate of response rate and 95% equal-tailed CrI.

A Bayesian hierarchical model was used to estimate the posterior probability of response rate for each group incorporating the baseline analysis stratification factors.[1]

Model for each group:

$Number\ of\ responders\ r_g \sim Binomial(n_g, p_g)$, g = 1, 2, 3, 4

$\theta_g = logit(p_g) = \log(p_g/(1-p_g)) = \gamma_0 + \gamma_1 I_{\{B1+\}} + \gamma_2 I_{\{B2+\}} + \psi_g$, g = 1, 2, 3, 4

Where γ_0, γ_1, γ_2, ψ_g are all parameters. Thus,

$\theta_1 = \gamma_0 + \psi_1$

$\theta_2 = \gamma_0 + \gamma_1 + \psi_2$

$\theta_3 = \gamma_0 + \gamma_2 + \psi_3$

$\theta_4 = \gamma_0 + \gamma_1 + \gamma_2 + \psi_4$

Priors:

$\gamma_k \sim Normal(0, 10^6)$, k = 0, 1, 2

$\psi_g \sim Normal(0, \omega^2)$, g = 1, 2, 3, 4

$\omega \sim Half-normal(1)$

Where we define r_g as the number of responders among n_g participants, p_g as the response rate r_g/n_g , θ_g as the log odds of treatment response $\log(p_g/(1-p_g))$, index g = 1,.,4 refers to the stratum

number, γ_k represent fixed effects of baseline analysis stratification factors (see below), and ψ_g denotes a random effect in stratum g.

The priors were selected to represent the vague information about prior beliefs and to have a small impact on the posterior distribution. Given that the priors were specifically selected to be non-informative and have minimal impact on the analysis, evaluation of sensitivity of results to the choice of priors was not performed.

The four analysis strata and representation of the two baseline analysis stratification factors B1 and B2 in the model are shown in **Table S4**.

Table S4. Baseline Stratification Factors for Four Stratum.

Stratum	**B1: HBsAg ($I_{\{B1+\}}$)**	**B2: HBeAg ($I_{\{B2+\}}$)**
1: HBsAg ≦3 log IU/mL and Negative HBeAg	B_{1-} (≦3 log IU/mL) (0)	B_{2-} (Negative) (0)
2: HBsAg >3 log IU/mL and Negative HBeAg	B_{1+} (>3 log IU/mL) (1)	B_{2-} (Negative) (0)
3: HBsAg ≦3 log IU/mL and Positive HBeAg	B_{1-} (≦3 log IU/mL) (0)	B_{2+} (Positive) (1)
4: HBsAg >3 log IU/mL and Positive HBeAg	B_{1+} (>3 log IU/mL) (1)	B_{2+} (Positive) (1)

For each group, the posterior distribution of response rate $P(p_g|\text{data})$, g=1,2,3,4 was derived for each stratum using the model specified above.

The posterior distribution of the group-level response rate was derived using a mixture of the posterior distributions of response rate for each analysis stratum in that group. The weights are proportional to the sample size of each stratum.

For some models with low number of events (0–1 event), the stratified Bayesian hierarchical model did not converge. In such cases, a reduced model that did not consider baseline stratification was fitted as a post-hoc analysis. The model estimated the point estimate and 95% highest posterior density credible interval of proportion of participants achieving the primary endpoint assuming the number of responders followed a binomial distribution:

$Number\ of\ responders\ r \sim Binomial(n, p)$

Where p is the response rate, with a non-informative (Jeffrey's) prior:

$p \sim \text{Beta}(0.5, 0.5)$The posterior distribution for p is:

$P(p|y, N) \sim \text{Beta}\ (y + 0.5, N - y + 0.5)$

Reference

1. Jones HE, Ohlssen DI, Neuenschwander B, Racine A, Branson M. Bayesian models for subgroup analysis in clinical trials. Clin Trials 2011;8:129–143.

Pre-specified subgroup analyses

The pre-specified subgroups for the primary outcome are described in **Table S5**.

Subgroup analyses were limited to descriptive statistics (n [%]); no statistical comparison between subgroups was planned.

Table S5. Pre-specified Subgroups for the Primary Outcome.

Subgroup	**Categories**
HBeAg Status	Positive or Negative
Baseline HBsAg (log10 IU/mL)	Low (≤3 log10 IU/mL); High (>3log10 IU/mL) ≤3; >3–3.5; >3.5–4; >4 Low (≤3000 IU/mL); High (3000 IU/mL)
Baseline HBV DNA level (log10 IU/mL)	For participants receiving NA therapy: - Not applicable For participants not receiving NA therapy: - ≤6; >6 - ≤4; >4–≤6; >6
Age group	**EMA:** <18; ≥18–64; ≥65–84; ≥85 **FDAAA:** ≤18; ≥19–64; ≥65 **Clinical and Epi (Group 1):** <50; ≥50
Sex	Male; Female
Race	American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White If enough data are available (≥5 participants per subgroup per treatment group) Asian may be further categorized as Asian – Central/South Asian Heritage; Asian – Japanese Heritage; Asian – East Asian Heritage; Asian – South East Asian Heritage or a combination of these, and White may be further categorized as White – Arabic/North African Heritage; White – White/Caucasian/European Heritage
Baseline viral genotype	For participants receiving NA therapy: - B; C; Other; Unknown For participants not receiving NA therapy:

Subgroup	Categories
	- B; C; Other; Unknown. If enough data are available (≥5 participants per subgroup per treatment group), Other may be further categorized into observed genotypes
Baseline substitution in the binding site	For participants not receiving NA therapy only: Present; Absent
Baseline BMI	<30; ≥30
Baseline ALT	≤ULN; >ULN
Baseline METAVIR Fibrosis Score	If enough data are available (≥5 participants per subgroup per treatment group): F0–F2; F3
For participants receiving NA therapy only: Time on current NA	<3 years; ≥3 years
For participants receiving NA therapy only: Type of NA	TAF&TDF vs Entecavir vs Other
For treatment naïve group only: Immune tolerance	For participants not receiving NA therapy: Immune-tolerant; Not immune-tolerant Participants are defined as immune tolerant if they meet all of the following criteria: Treatment naïve (i.e. no prior medications reported on the Prior Medications CRF), HBeAg positive (≥0.09 U/mL), ALT normal (≤33 IU/L in females; ≤40 IU/L in males) and HBV DNA >10^6 IU/mL
Duration of Hep B Infection	<5 years, ≥5–<10 years, ≥10–<20 years, ≥20 years
Phase of HBV Infection (Strict Criteria)	Phase 1; Phase 2; Other HBeAg-positive; Phase 3; Phase 4; Other HBeAg-negative, where phases are defined as below. - Phase 1 = HBeAg-positive, ALT ≤ULN during screening and at baseline, HBV DNA >10^6 IU/ml during screening and at baseline

Subgroup	Categories
	- Phase 2 = HBeAg-positive, ALT >ULN either during screening or at baseline, HBV DNA >10^4 IU/ml during screening and at baseline - Other HBeAg-positive = HBeAg-positive, neither Phase 1 nor Phase 2 - Phase 3 = HBeAg-negative, ALT ≤ULN during screening and at baseline, HBV DNA <20,000 IU/ml during screening and at baseline - Phase 4 = HBeAg-negative, ALT >ULN either during screening or at baseline, HBV DNA >2,000 IU/ml during screening and at baseline - Other HBeAg-negative = HBeAg-negative, neither Phase 3 nor Phase 4
Phase of HBV Infection (Loose Criteria)	Phase 1 loose; Phase 2 loose; Phase 3 loose; Phase 4 loose, where phases are defined as below. - Phase 1 loose= HBeAg-positive, ALT ≤ULN during screening and at baseline - Phase 2 loose = HBeAg-positive, ALT >ULN either during screening or at baseline - Phase 3 loose = HBeAg-negative, ALT ≤ULN during screening and at baseline - Phase 4 loose = HBeAg-negative, ALT >ULN either during screening or at baseline
HBV RNA level	Target not detected; Target detected
HBcrAg	Low (≤3 log10 U/mL); High (>3 log10 U/mL)

ALT, alanine aminotransferase; BMI, body mass index; CRF, case report form; DNA, deoxyribonucleic acid; EMA, European Medicines Agency; FDAAA, Food and Drug Administration Amendments Act; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; METAVIR, meta-analysis of histological data in viral hepatitis; NA, nucleos(t)ide analogue; RNA, ribonucleic acid; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

Supplementary Results

Difference in primary outcome between treatment groups

At 24 weeks post end of treatment (EoT), the difference in the proportion of participants receiving NA therapy who achieved the primary outcome was 0% (95% CrI −27%, 37%), −6% (95% CrI −28%, 8%), and −6% (95% CrI −41%, 11%) between Groups 1 and 2, Groups 1 and 3, and Groups 2 and 3, respectively. The posterior probability that this difference was greater than −5% was 66%, 54%, and 66%, respectively.

At 24 weeks post EoT, the difference in the proportion of participants not receiving NA therapy who achieved the primary outcome between Groups 1 and 2 was −4% (95% CrI −31%, 19%). The posterior probability that this difference was greater than −5% was 58%. No other between-treatment group comparisons were performed due to the low number of responders.

ALT changes

ALT increases were observed in both participants receiving NA therapy and participants not receiving NA therapy (**Table S6**).

Table S6. Summary of Participants with Hepatobiliary Laboratory Abnormalities.

Laboratory criteria	**Participants receiving NA therapy (n=226)**	**Participants Not Receiving NA Therapy (n=230)**
n	225	227
ALT ≥3 x ULN and BIL ≥2 x ULN	0	2 (<1)*
ALT ≥3 x ULN and INR >1.5	0	0
ALT ≥3 x ULN	39 (17)	93 (41)

*1 participant had Gilbert's syndrome and had an increase in ALT and total bilirubin not significantly different from baseline; 1 participant had an ALT and bilirubin increase that was reported as an SAE (hepatitis B flare) and the participant was withdrawn from treatment.

ALT, alanine aminotransferase; BIL, bilirubin; INR, international normalized ratio; NA, nucleos(t)ide analogue; SAE, serious adverse event; ULN, upper limit of normal.

The protocol included monitoring and stopping criteria for participants with ALT >3x ULN. Of the 132 participants with ALT increase ≥3x ULN, the flares were transient. The majority occurred within the first 12 weeks of treatment and were associated with concurrent decline in HBsAg. Two were associated with an increase in bilirubin >2x ULN. Detailed review of these cases did not identify drug induced liver toxicity. In all other participants, the ALT was not associated with other changes in laboratory values to indicate liver toxicity (bilirubin, INR, alkaline phosphatase). A minority of ALT increases were observed in participants during the off-treatment period. The ALT increases were reviewed with external experts, who concluded that the most likely explanation for the ALT increases was a therapeutic effect of bepirovirsen (where there was a temporal association with HBsAg/HBV DNA decreases) or fluctuations in underlying disease activity (for cases in the off-treatment period). Drug-induced liver injury was not considered the most likely explanation in any of the cases. The maximum ALT increase was 30 x ULN (1264 IU/L). Bilirubin and alkaline phosphatase were normal throughout; INR was 1.2 at screening and a week after reaching the peak ALT, indicating no liver insufficiency.

The proportion of participants within each ALT category over time is shown in **Figure S1**.

Figure S1. Proportion of Participants Within ALT Categories (≤ULN, >ULN to ≤3xULN, >3xULN to ≤5xULN, >5xULN to ≤10xULN, >10xULN) Over Time in (A) Participants Receiving NA Therapy and (B) Participants Not Receiving NA Therapy (ITT Population).

ALT, alanine aminotransferase; ITT, intent-to-treat; NA, nucleos(t)ide analogue; OT, off-treatment; QW, once a week; ULN, upper limit of normal.

Liver-related SAE narratives

Hepatitis B flare SAE:

A 54-year-old female participant, enrolled in the cohort of participants not receiving NA therapy, developed grade 3 hepatitis B flare after 125 days of treatment with bepirovirsen.

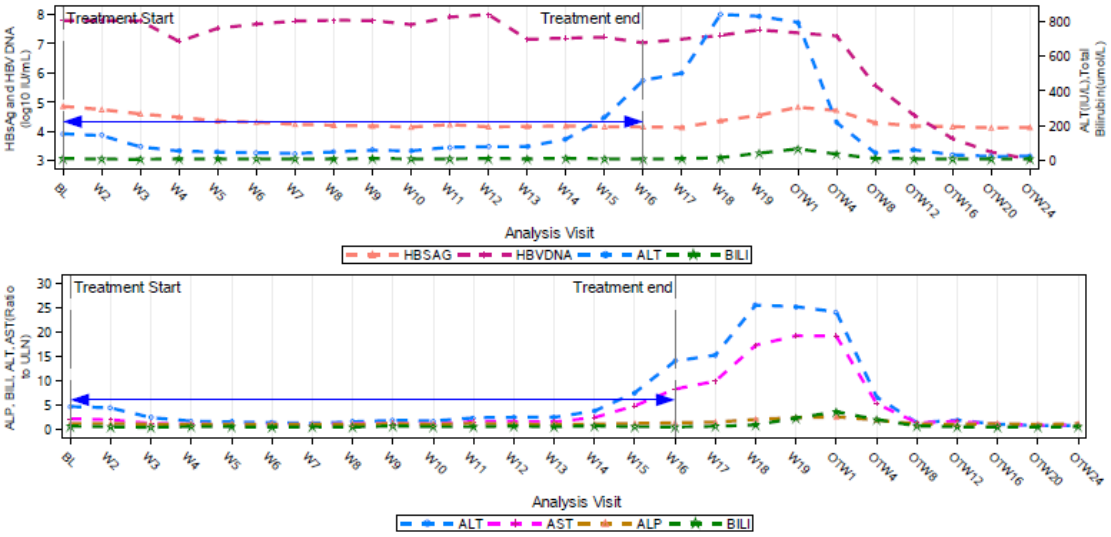
The HBV DNA was 7.35 log at screening and 7.78 log at baseline. The ALT at screening was 40 IU/L (normal range: 10–33 IU/L) and 154 IU/L at baseline (prior to the first administration of bepirovirsen). At Week 16, the ALT had increased to 461 IU/L. At Week 16, the total bilirubin was 0.53 mg/dL (normal range <1.1 mg/dL). Bepirovirsen dose was held from Week 17. The participant visited the site for increased monitoring of liver chemistries as per protocol. The participant was admitted to hospital approximately 3.5 weeks after treatment was held with a further increase in ALT (794 IU/L) and a concurrent increase in bilirubin (3.94 mg/dL) noted. The participant also noted to have symptoms of loss of appetite, increasing fatigue/lethargy and worsening shortness of breath on exertion.

An SAE was reported as hepatitis B flare (grade 3).

The participant was treated with tenofovir, prednisolone, Gaviscon, folic acid and nexium.

Treatment with bepirovirsen was discontinued. The SAE was reported as recovered/resolved by end of study.

The participant's HBsAg, HBV DNA, ALT, AST, ALP and bilirubin profiles over the course of the study are shown below. The participant's HBsAg at baseline was 71480 (4.85 log) IU/mL; HBsAg at the time of treatment hold on Week 17 was 13679 (4.14 log) IU/mL; HBsAg nadir of 13262 (4.12 log) IU/mL occurred at the off-treatment Week 20 visit.



ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASP, aspartate aminotransferase; BIL, bilirubin; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Hepatic function abnormal SAE:

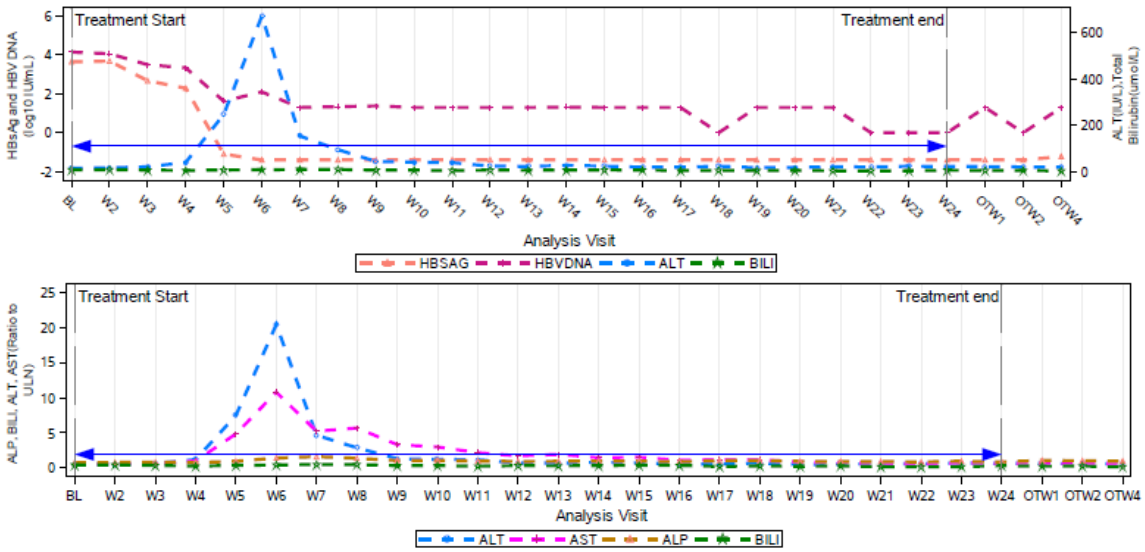
A 26-year-old female participant, enrolled in the cohort of participants not receiving NA therapy, developed grade 4 hypohepatia (preferred term: hepatic function abnormal) after 35 days of treatment with bepirovirsen.

Baseline ALT was 15 IU/L (normal range: 10–33 IU/L). At Week 5, the ALT had increased to 247 IU/L. At Week 6, the ALT had increased to 672 IU/L. The participant was hospitalized after Week 6 with symptoms of poor appetite with nausea and palpitation and weight loss. Study treatment was held.

There was no concurrent increase in bilirubin. The participant was treated with magnesium isoglycyrrhizinate (150 mg/kg), monoammonium glycyrrhizinate cysteine sodium chloride injection (200 ml, IV), diammonium glycyrrhizinate (150 mg/kg TID), bicyclol tablet (50mg, oral, TID), inosine injection (0.4g IV) and vitamin C injection (3000 mg/kg).

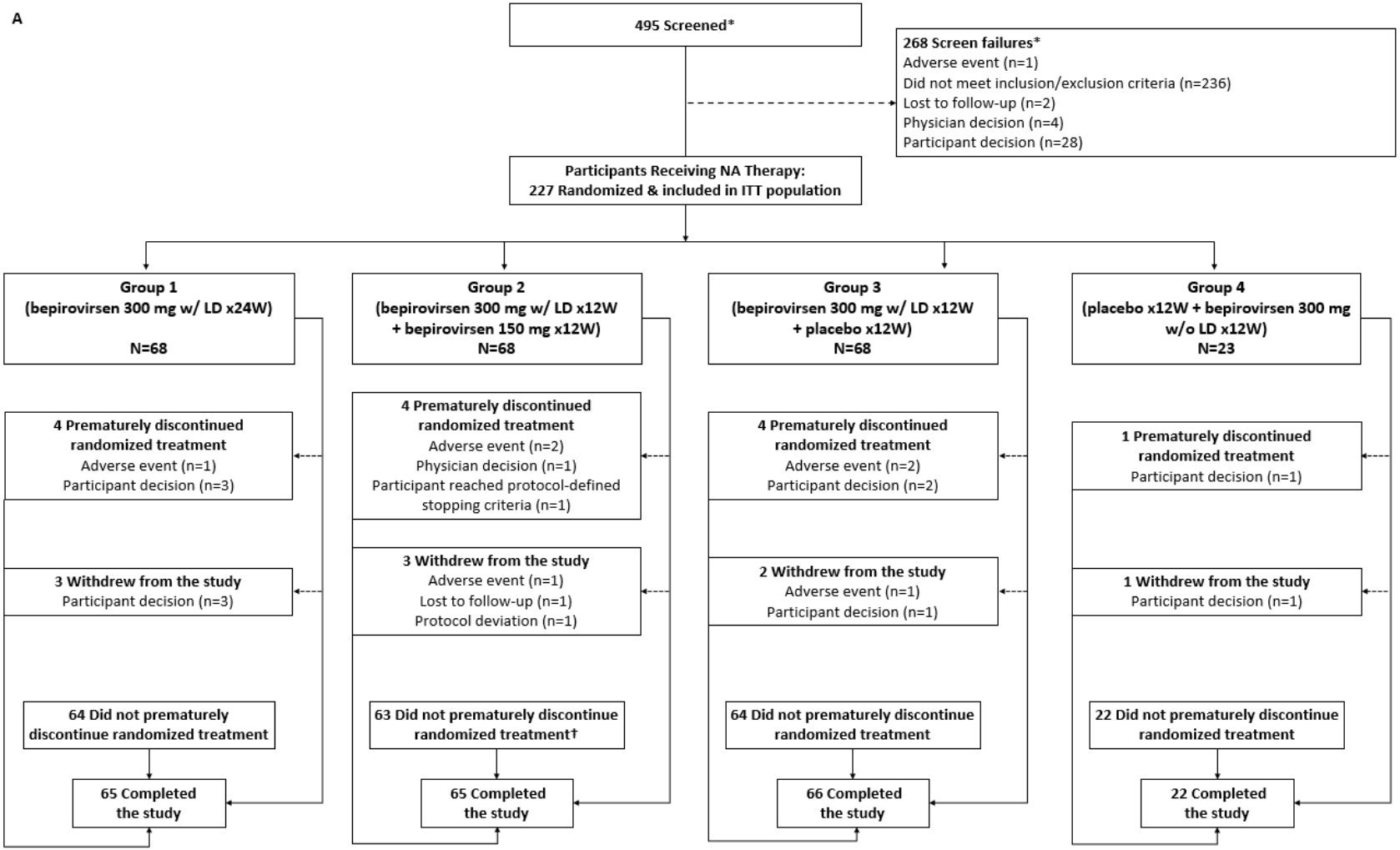
During admission the participant was in good condition and had a significant decrease in ALT and therefore was discharged from hospital. Treatment with bepirovirsen was continued on Week 8, as per protocol at a reduced dose of 150 mg per week. The SAE was reported as recovered/resolved by end of study.

The participant's HBsAg, HBV DNA, ALT, AST, ALP and bilirubin profiles over the course of the study are shown below. The participant's HBsAg at baseline was 4394 (3.64 log) IU/mL; HBsAg at the time of treatment hold on Week 6 was <0.05 IU/mL and was maintained until off treatment Week 4, where HBsAg became quantifiable.

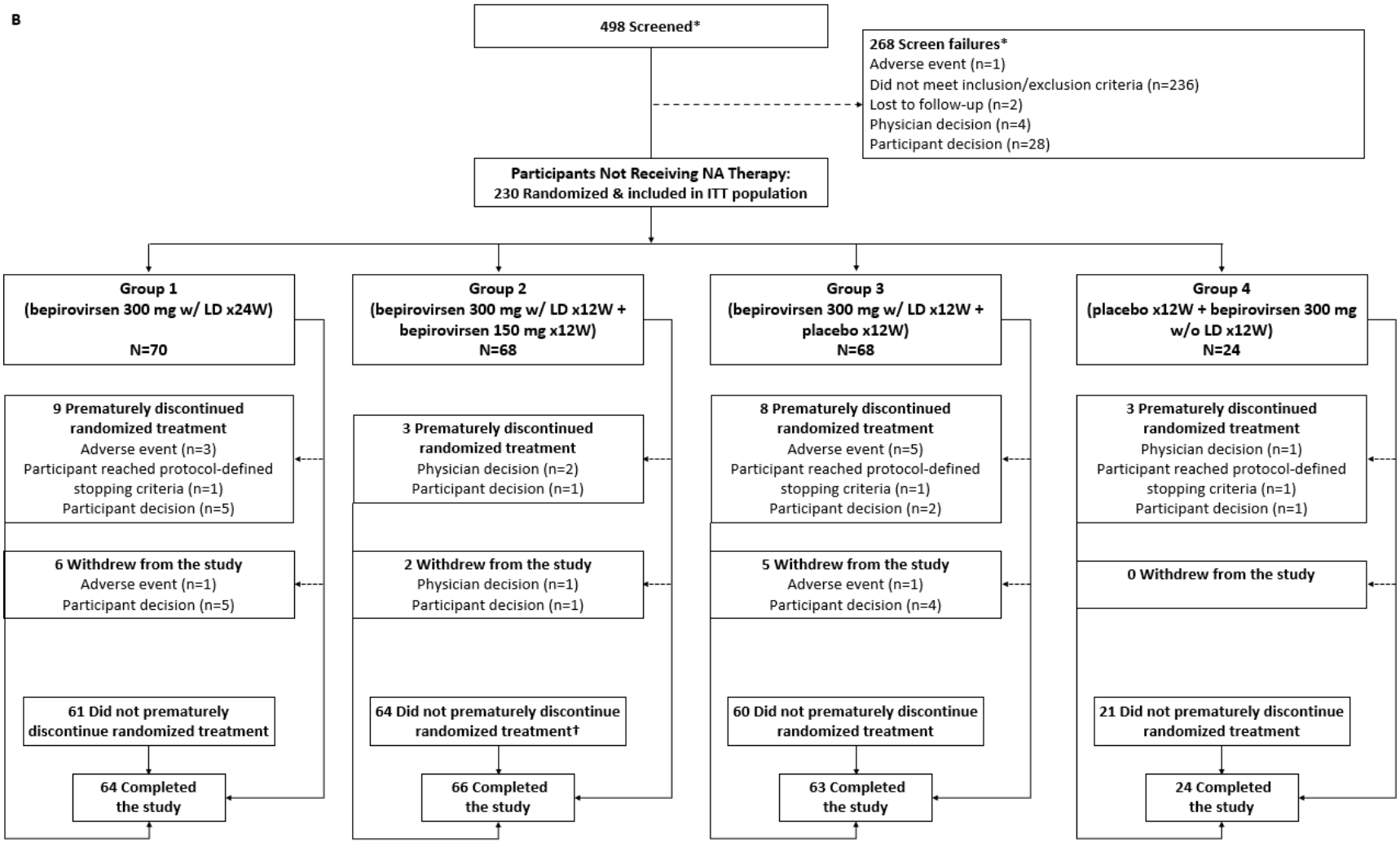


ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASP, aspartate aminotransferase; BIL, bilirubin; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Figure S2. Participant Disposition for the (A) Participants Receiving NA Therapy and (B) Participants Not Receiving NA Therapy.



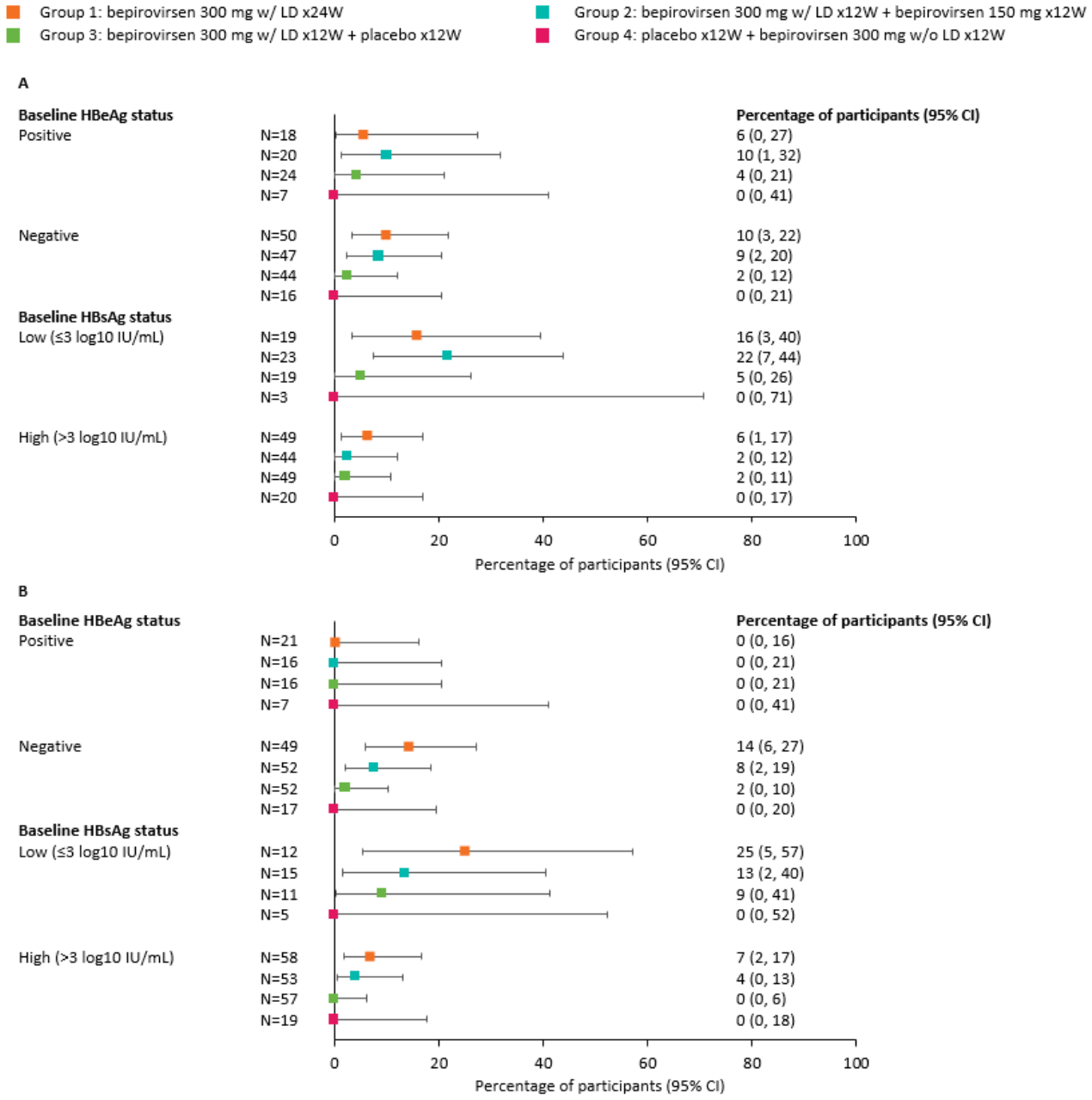
B


498 Screened*
268 Screen failures*
Adverse event (n=1)
Did not meet inclusion/exclusion criteria (n=236)
Lost to follow-up (n=2)
Physician decision (n=4)
Participant decision (n=28)
Participants Not Receiving NA Therapy:
230 Randomized & included in ITT population
Group 1
(bepirovirsen 300 mg w/ LD x24W)
N=70
Group 2
(bepirovirsen 300 mg w/ LD x12W + bepirovirsen 150 mg x12W)
N=68
Group 3
(bepirovirsen 300 mg w/ LD x12W + placebo x12W)
N=68
Group 4
(placebo x12W + bepirovirsen 300 mg w/o LD x12W)
N=24
9 Prematurely discontinued randomized treatment
Adverse event (n=3)
Participant reached protocol-defined stopping criteria (n=1)
Participant decision (n=5)
3 Prematurely discontinued randomized treatment
Physician decision (n=2)
Participant decision (n=1)
8 Prematurely discontinued randomized treatment
Adverse event (n=5)
Participant reached protocol-defined stopping criteria (n=1)
Participant decision (n=2)
3 Prematurely discontinued randomized treatment
Physician decision (n=1)
Participant reached protocol-defined stopping criteria (n=1)
Participant decision (n=1)
6 Withdrew from the study
Adverse event (n=1)
Participant decision (n=5)
2 Withdrew from the study
Physician decision (n=1)
Participant decision (n=1)
5 Withdrew from the study
Adverse event (n=1)
Participant decision (n=4)
0 Withdrew from the study
61 Did not prematurely discontinue randomized treatment
64 Did not prematurely discontinue randomized treatment†
60 Did not prematurely discontinue randomized treatment
21 Did not prematurely discontinue randomized treatment
64 Completed the study
66 Completed the study
63 Completed the study
24 Completed the study

*NA therapy data were not collected during screening, so screening failures (n=268) are duplicated across participants receiving NA therapy and participants not receiving NA therapy. The total number of participants screened was n=725. As NA status (receiving NA therapy or not receiving NA therapy) was not collected at screening, the screening numbers for each population are derived by adding the number of screening failures to the number of participants randomized and included in the ITT. †In Group 2, one participant each in the population receiving NA therapy and the population not receiving NA therapy did not receive any treatment. There is overlap in some instances between participants who withdrew from the study and those who permanently discontinue study treatment.

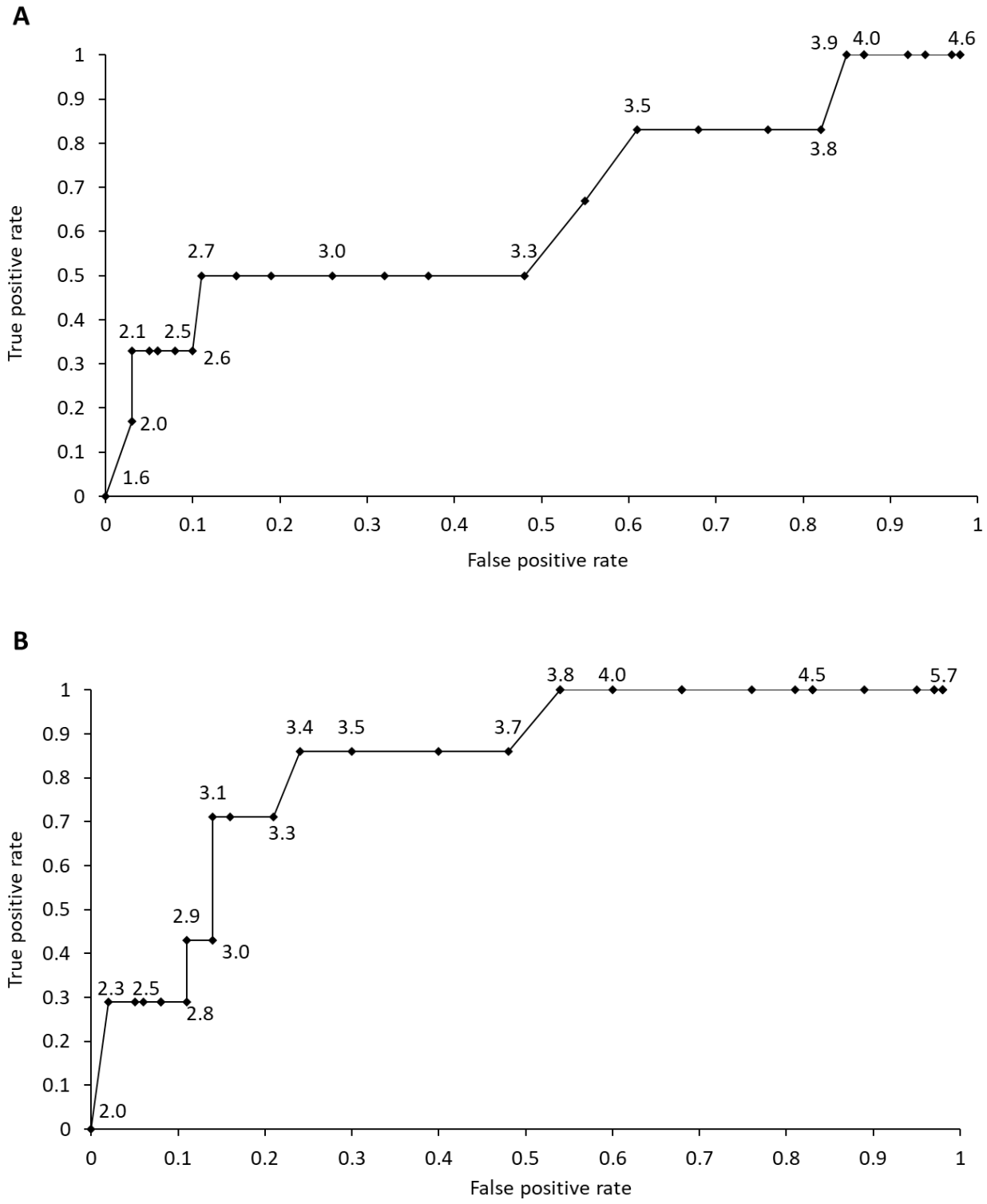
ITT, intent-to-treat; LD, loading dose; NA, nucleos(t)ide analogue; W, week.

Figure S3. Proportion of Participants (A) Receiving NA Therapy and (B) Not Receiving NA Therapy, Achieving the Primary Outcome by Baseline HBeAg and HBsAg status (ITT Population).



CI, confidence interval; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; ITT, intent-to-treat; LD loading dose; NA, nucleos(t)ide analogue; W, week; w/, with; w/o, without.

Figure S4. Receiver Operating Characteristic Analysis for Baseline HBsAg as a Predictor of Primary Outcome Achievement in Participants in Group 1 Who Reached End-of-Study in (A) Participants Receiving NA Therapy and (B) Participants Not Receiving NA Therapy (ITT Population).



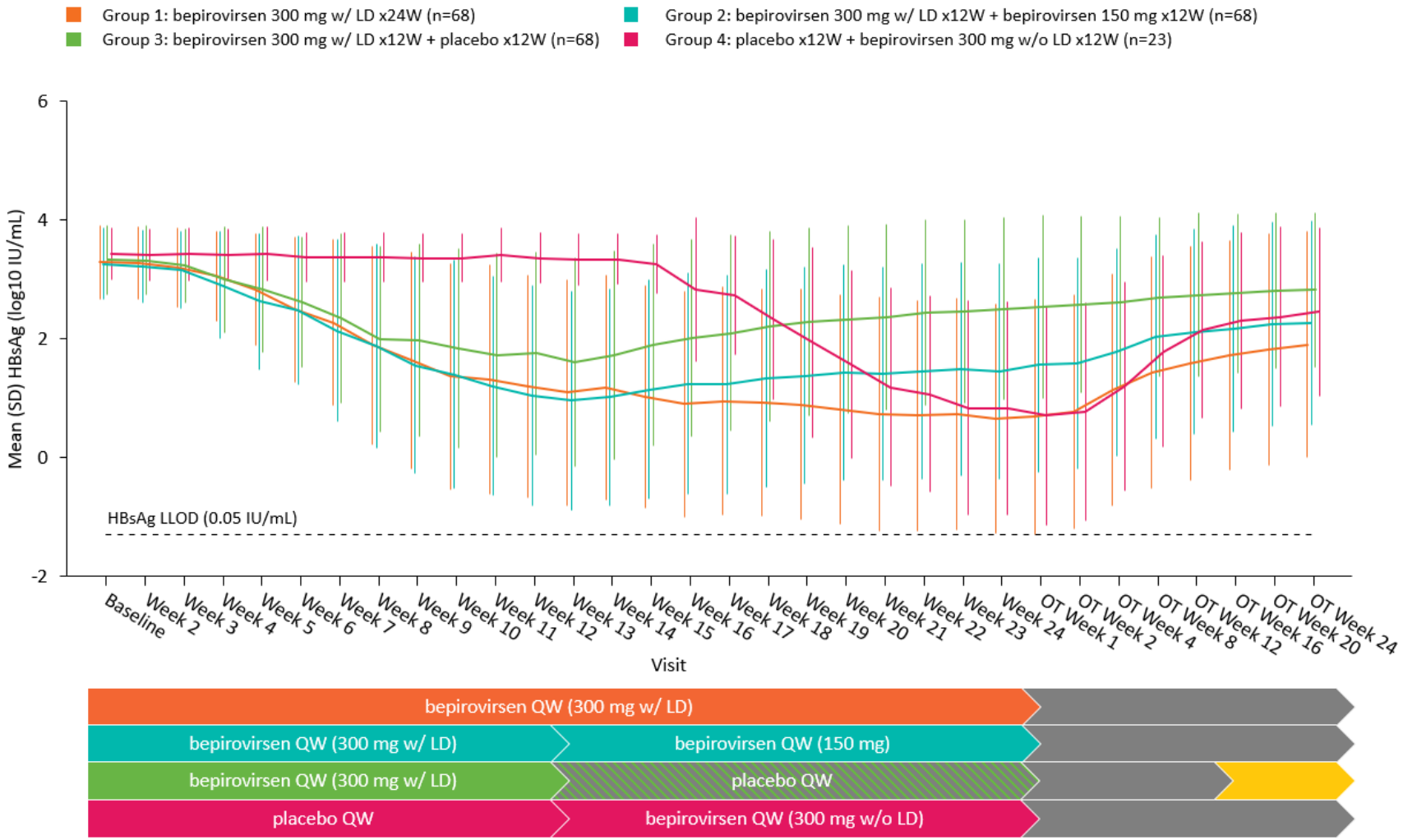
Data labels on the graphs indicate baseline HBsAg level (log10 IU/mL).

Panel A: at HBsAg cut of 3.5 log10 IU/mL the specificity (1-false positive rate) is 0.39, sensitivity (true positive rate) is 0.83 and accuracy is 0.426.

Panel B: at HBsAg cut of 3.5 log10 IU/mL the specificity (1-false positive rate) is 0.70, sensitivity (true positive rate) is 0.86 and accuracy is 0.714.

HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue.

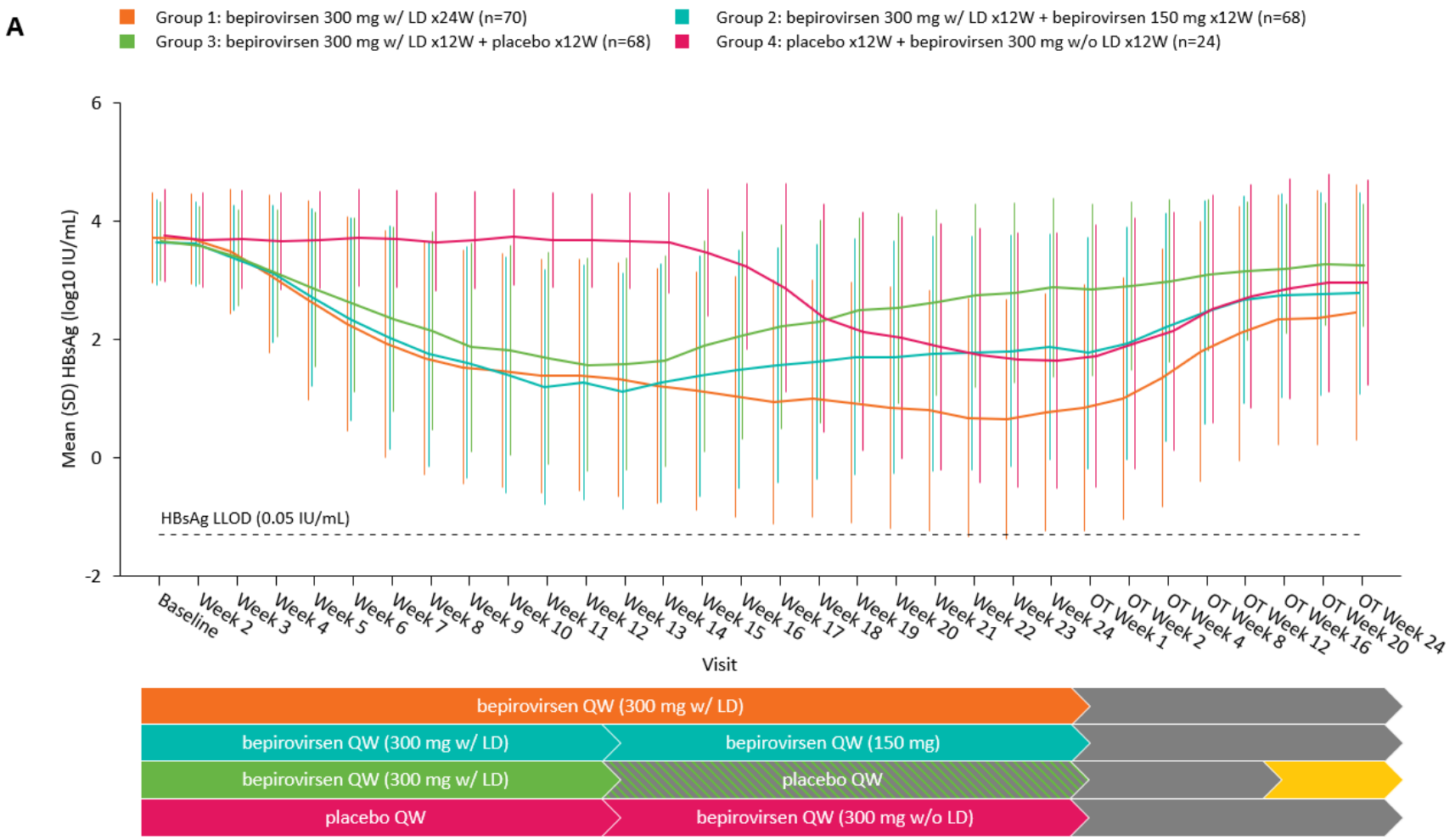
Figure S5. Mean HBsAg Levels Over Time in Participants Receiving NA Therapy (ITT Population).



Shaded gray arrows below the graph indicate 24-week off-treatment follow-up; shaded yellow arrow below the graph indicates additional follow-up in Group 3. Per protocol, participants receiving NA therapy were expected to continue their NA therapy throughout the study.

HBsAg, hepatitis B surface antigen; ITT, intent-to-treat; LD, loading dose; LLOD, lower limit of detection; NA, nucleos(t)ide analogue; OT, off-treatment; QW, once a week; W, week; w/=with; w/o=without.

Figure S6. Mean (A) HBsAg and (B) HBV DNA Levels Over Time in Participants Not Receiving NA Therapy (ITT Population).



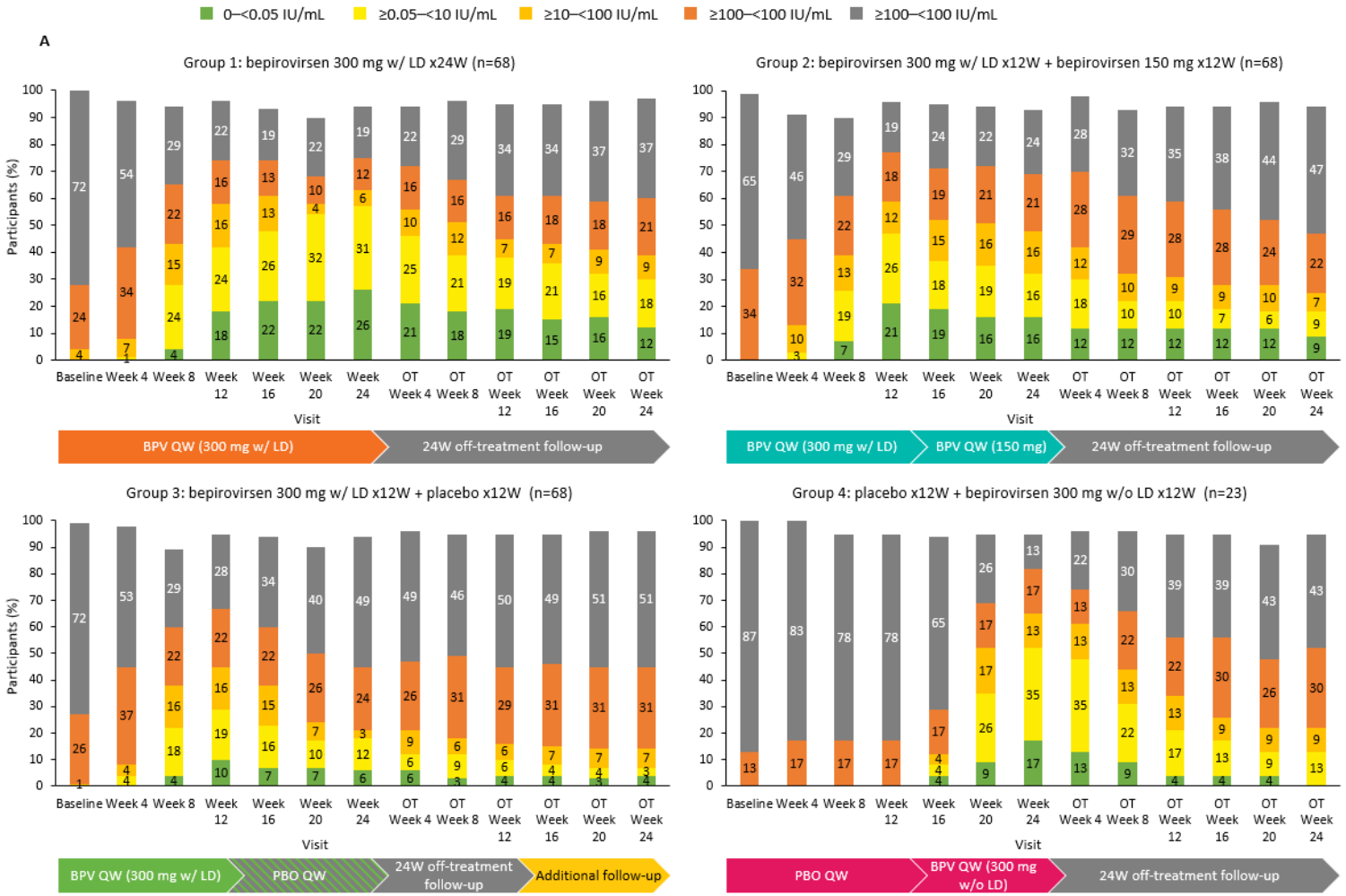
B

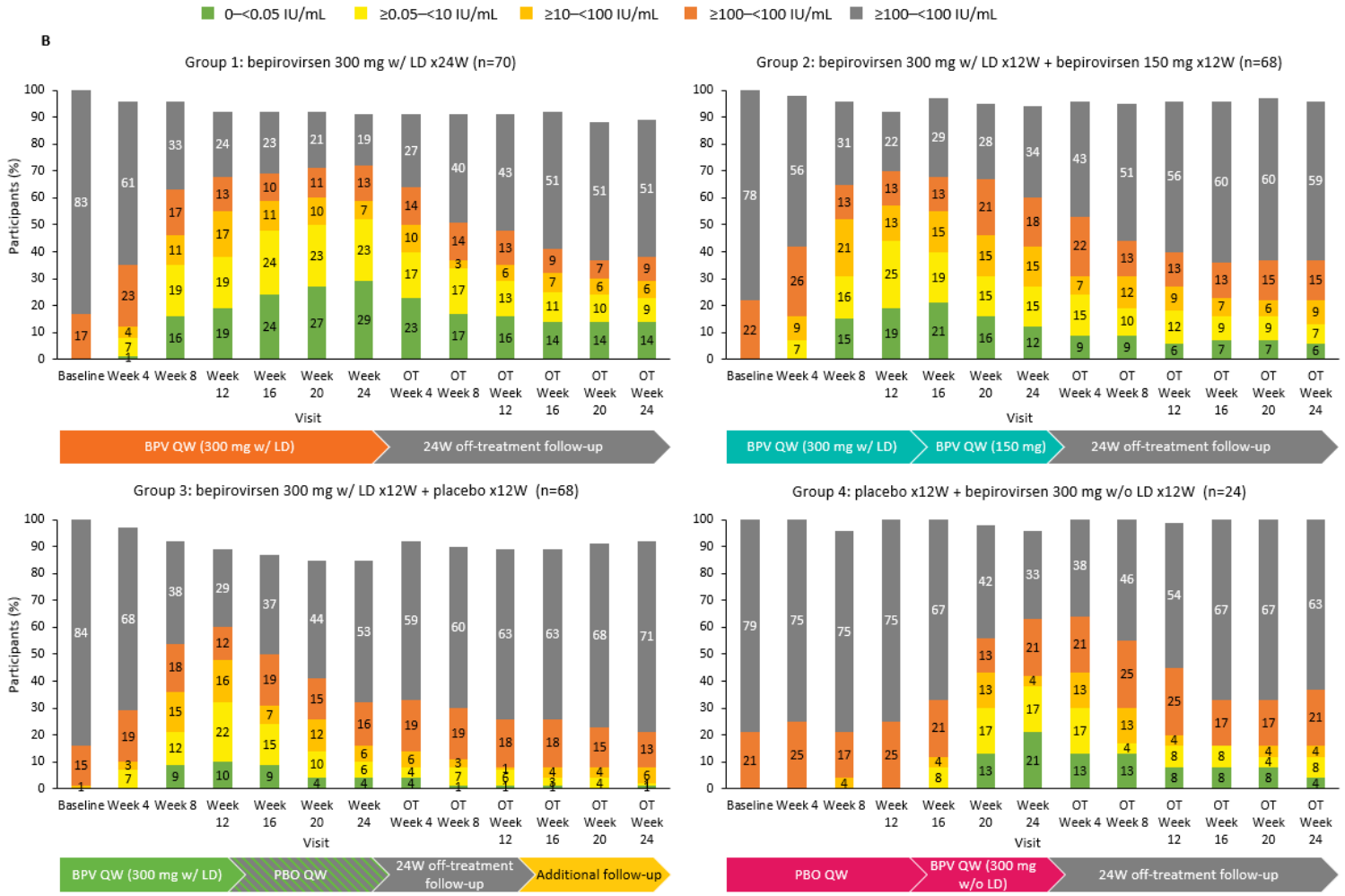

Group 1: bepirovirsen 300 mg w/ LD x24W (n=70)
Group 2: bepirovirsen 300 mg w/ LD x12W + bepirovirsen 150 mg x12W (n=68)
Group 3: bepirovirsen 300 mg w/ LD x12W + placebo x12W (n=68)
Group 4: placebo x12W + bepirovirsen 300 mg w/o LD x12W (n=24)
Mean (SD) HBV DNA (log10 IU/mL)
8
6
4
2
0
HBV DNA LLOQ (20 IU/mL)
Baseline
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Week 11
Week 12
Week 13
Week 14
Week 15
Week 16
Week 17
Week 18
Week 19
Week 20
Week 21
Week 22
Week 23
Week 24
OT Week 1
OT Week 2
OT Week 4
OT Week 8
OT Week 12
OT Week 16
OT Week 20
OT Week 24
Visit
bepirovirsen QW (300 mg w/ LD)
bepirovirsen QW (300 mg w/ LD)
bepirovirsen QW (150 mg)
bepirovirsen QW (300 mg w/ LD)
placebo QW
placebo QW
bepirovirsen QW (300 mg w/o LD)

Shaded gray arrows below the graphs indicate 24-week off-treatment follow-up; shaded yellow arrow below the graphs indicates additional off-treatment follow-up in Group 3.

DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ITT, intent-to-treat; LD, loading dose; LLOD, lower limit of detection; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; OT, off-treatment; QW, once a week; SD, standard deviation; W, week; w/=with; w/o=without.

Figure S7. Proportion of Participants Within HBsAg Categories (0–<0.05, ≥0.05–<10, ≥10–<100, ≥100–<1000, ≥1000 IU/mL) Over Time in (A) Participants Receiving NA Therapy and (B) Participants Not Receiving NA Therapy (ITT Population).





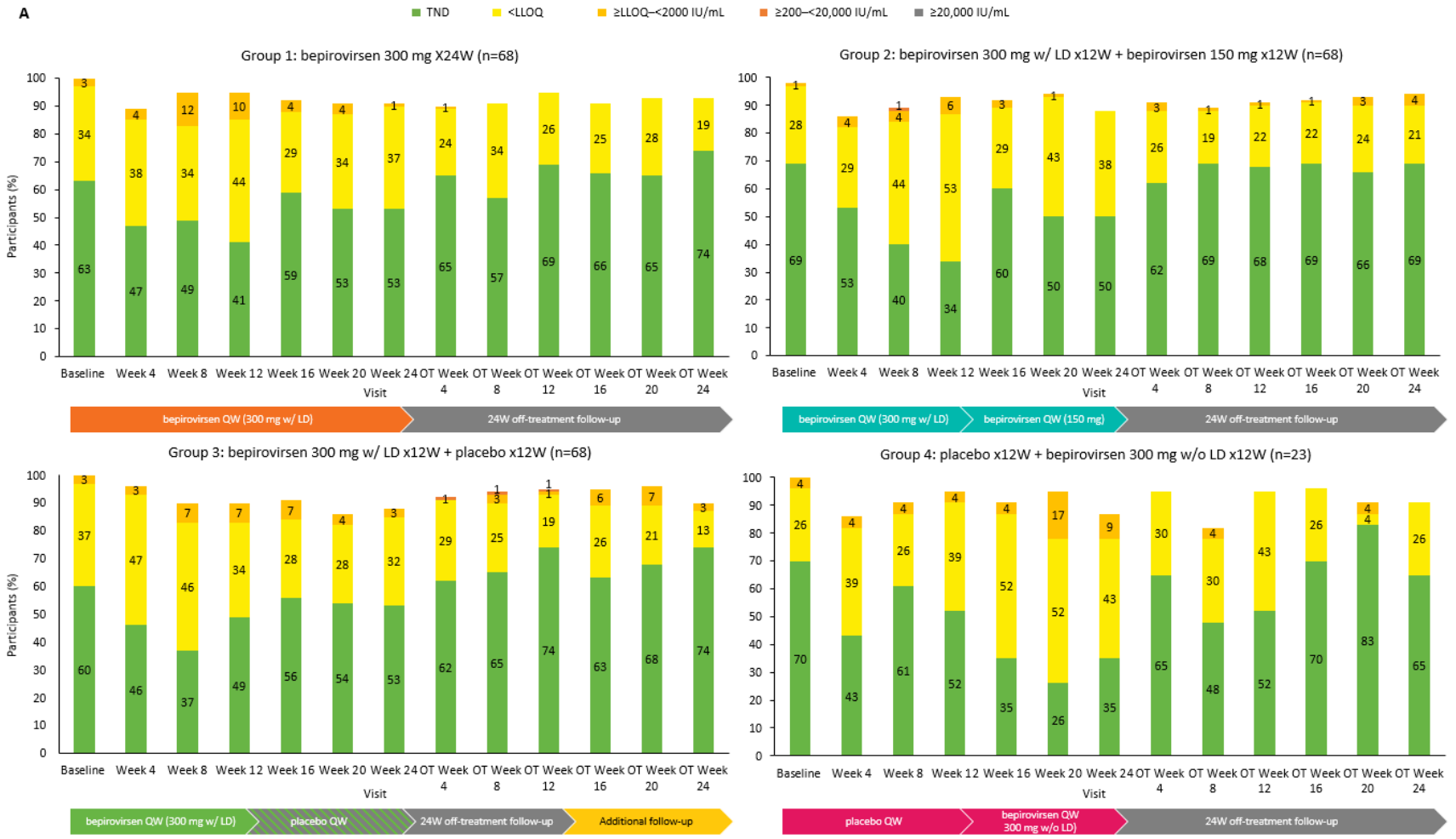
Percentages calculated based on the total number of participants in the ITT population (note: at the time of the EASL presentation,[1] percentages were calculated based on available data at the study visit of interest).

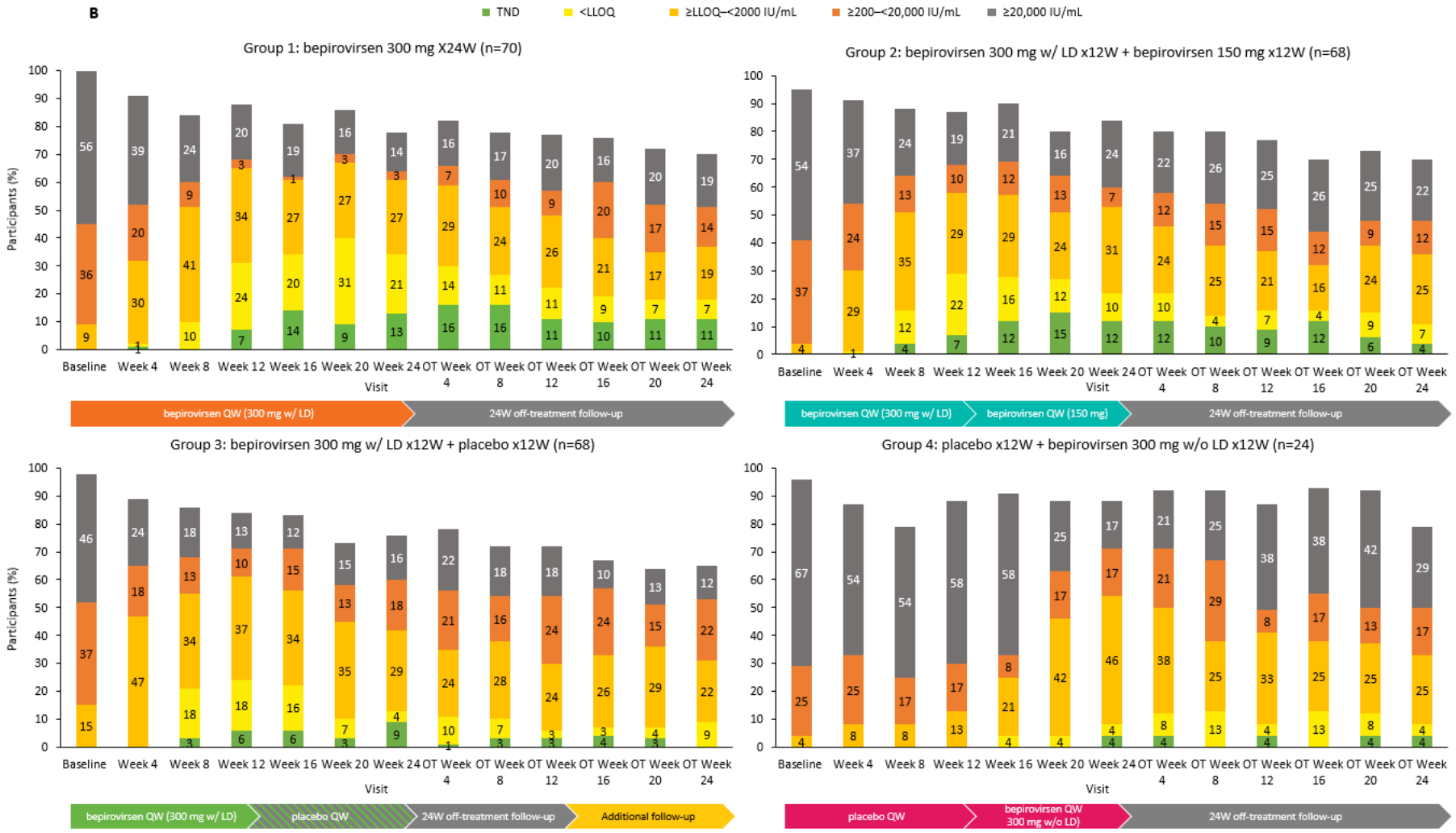
BPV, bepirovirsen; HBsAg, hepatitis B surface antigen; ITT, intent-to-treat; LD, loading dose; NA, nucleos(t)ide analogue; OT, off-treatment; PBO, placebo; QW, once a week; W, week; w/, with; w/o, without.

Reference

1. Yuen M, Lim S, Plesniak R, et al. Efficacy and safety of bepirovirsen in patients with chronic hepatitis B virus infection: interim results from the randomised phase 2b B-Clear study. European Association for the Study of the Liver - International Liver Congress (ILC 2022); 77(S1): S12-13 (LB004A and LB004B).

Figure S8. Proportion of Participants Within HBV DNA Categories (TND, <LLOQ, ≥LLOQ–<2000, ≥2000–<20,000, ≥20,000 IU/mL) Over Time in (A) Participants Receiving NA Therapy and (B) Participants Not Receiving NA Therapy (ITT Population).

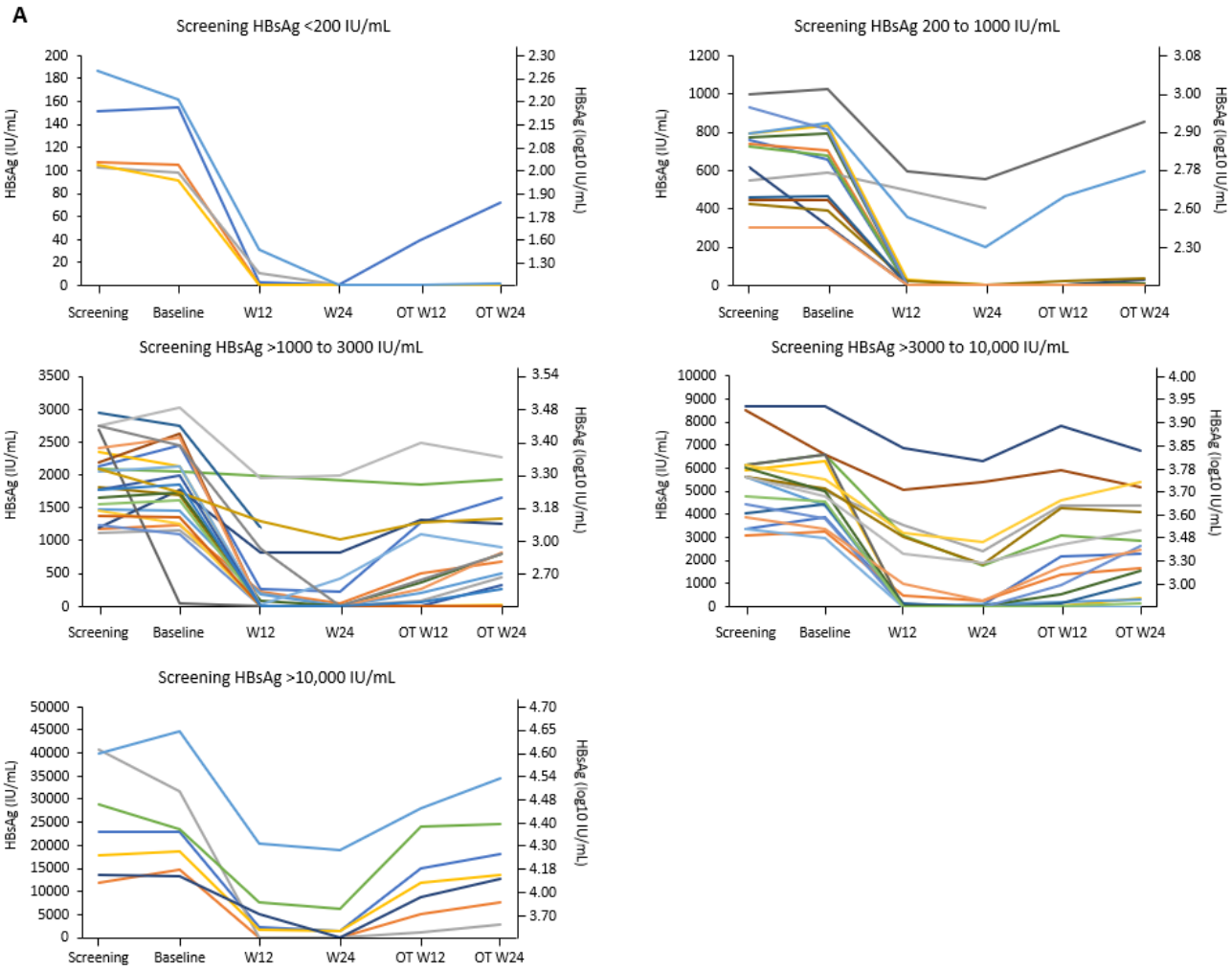




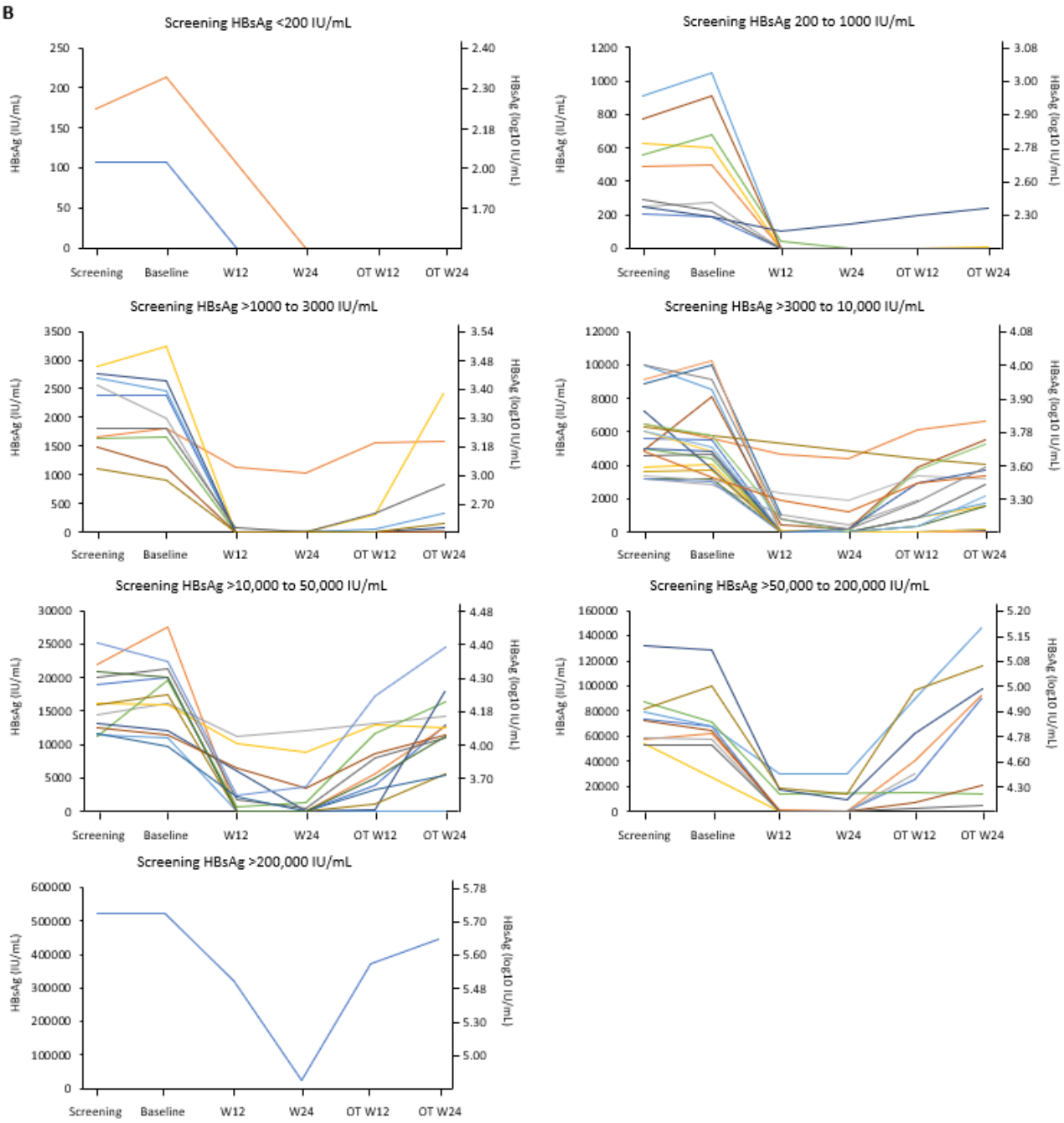
Panel B: values measured after rescue medication was initiated are excluded.

DNA, deoxyribonucleic acid; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; OT, off-treatment; QW, once a week; TND, target not detected.

Figure S9. Individual HBsAg Levels in Group 1 by Baseline HBsAg Concentration in (A) Participants Receiving NA Therapy and (B) Participants Not Receiving NA Therapy.



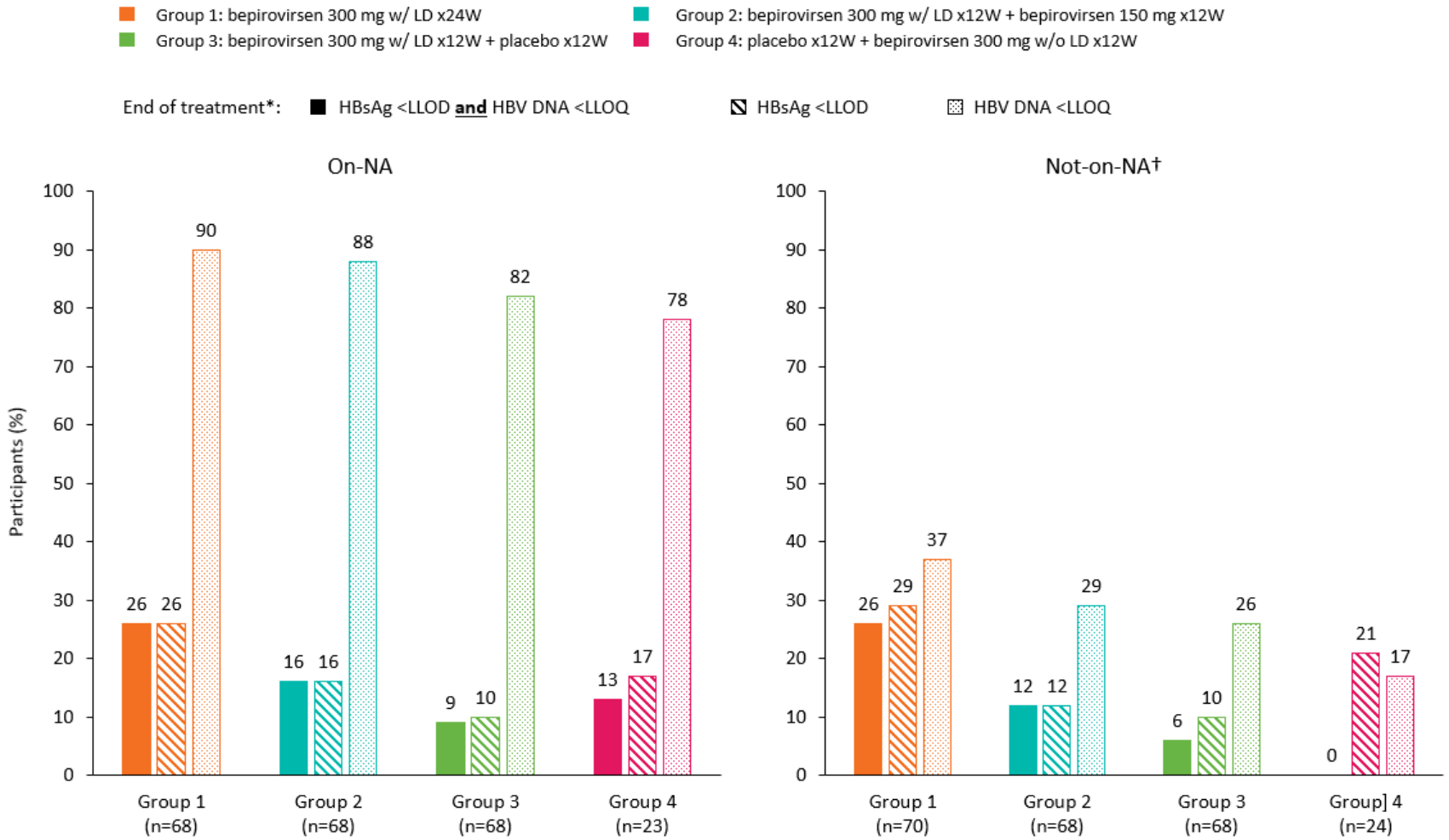
B



Data shown for participants with available screening HBsAg and at least one post-baseline value at the time points shown.

HBsAg, hepatitis B surface antigen; OT, off-treatment.

Figure S10. Proportion of Participants Achieving HBsAg <LLOD and HBV DNA <LLOQ in Groups 1–4 at End of Treatment (ITT Population).



*Week 24 for Groups 1, 2 and 4, Week 12 for Group 3; †34 (14.5%) participants received NA during the study. Percentages calculated based on the total number of participants in the ITT population (note: at the time of the EASL presentation[1], percentages were calculated based on available data at the end of treatment time point). Per protocol, participants receiving NA therapy were expected to continue their NA therapy throughout the study.

DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ITT, intent-to-treat; LD, loading dose; LLOD, lower limit of detection; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Reference

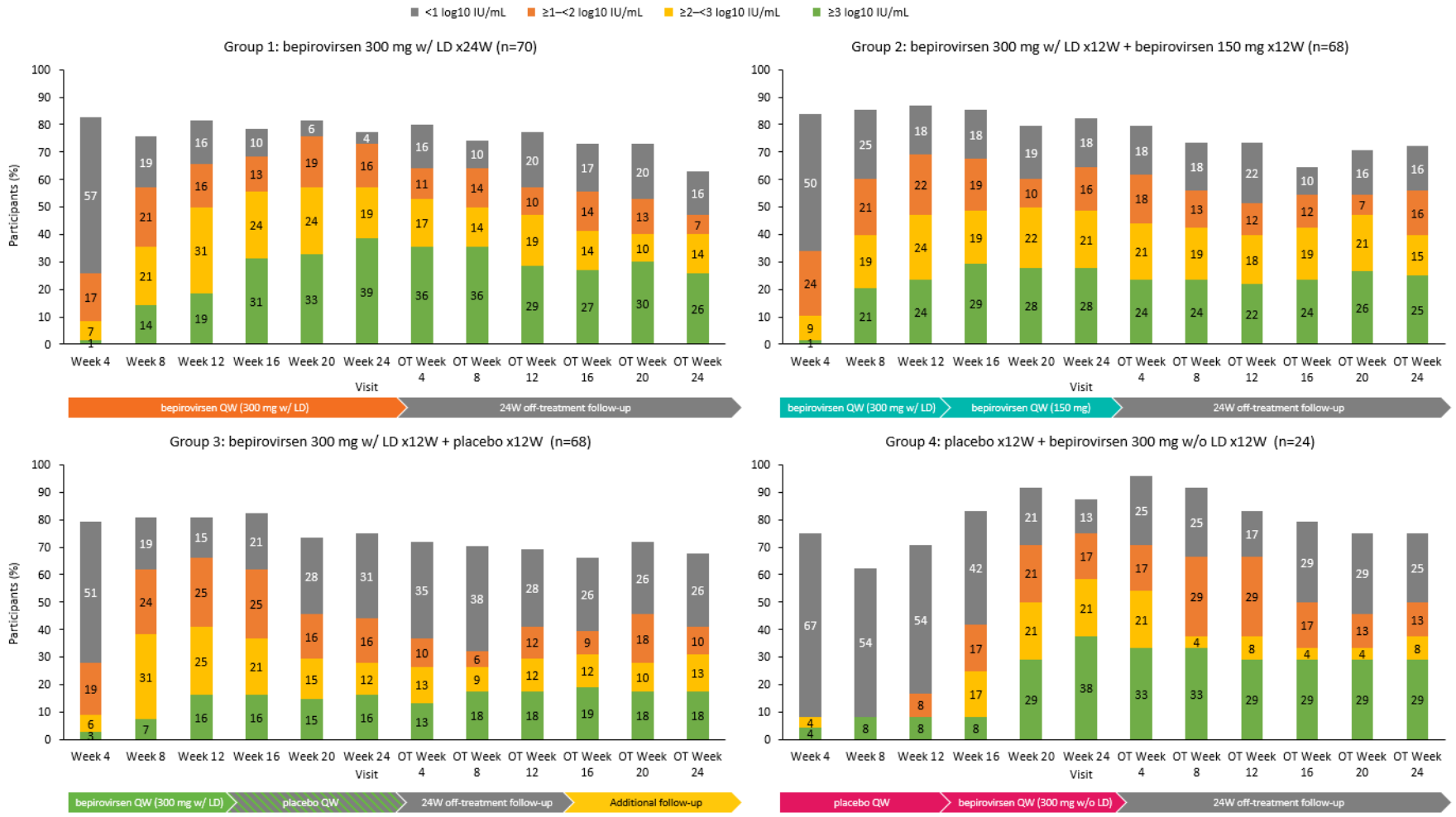
1. Yuen M, Lim S, Plesniak R, et al. Efficacy and safety of bepirovirsen in patients with chronic hepatitis B virus infection: interim results from the randomised phase 2b B-Clear study. European Association for the Study of the Liver - International Liver Congress (ILC 2022); 77(S1): S12-13 (LB004A and LB004B).

Figure S11. Categorical Changes from Baseline in HBsAg (i.e., reductions of <0.5, ≥0.5–<1, ≥1–<1.5, ≥1.5–<3, ≥3 log10 IU/mL) in (A) Participants Receiving NA Therapy and (B) Participants Not Receiving NA Therapy (ITT Population).

Panel A: Per protocol, participants receiving NA therapy were expected to continue their NA therapy throughout the study. Percentages calculated based on the total number of participants in the ITT population.

HBsAg, hepatitis B surface antigen; ITT, intent-to-treat; LD, loading dose; NA, nucleos(t)ide analogue; OT, off-treatment; QW, once a week; W, week; w/=with; w/o=without.

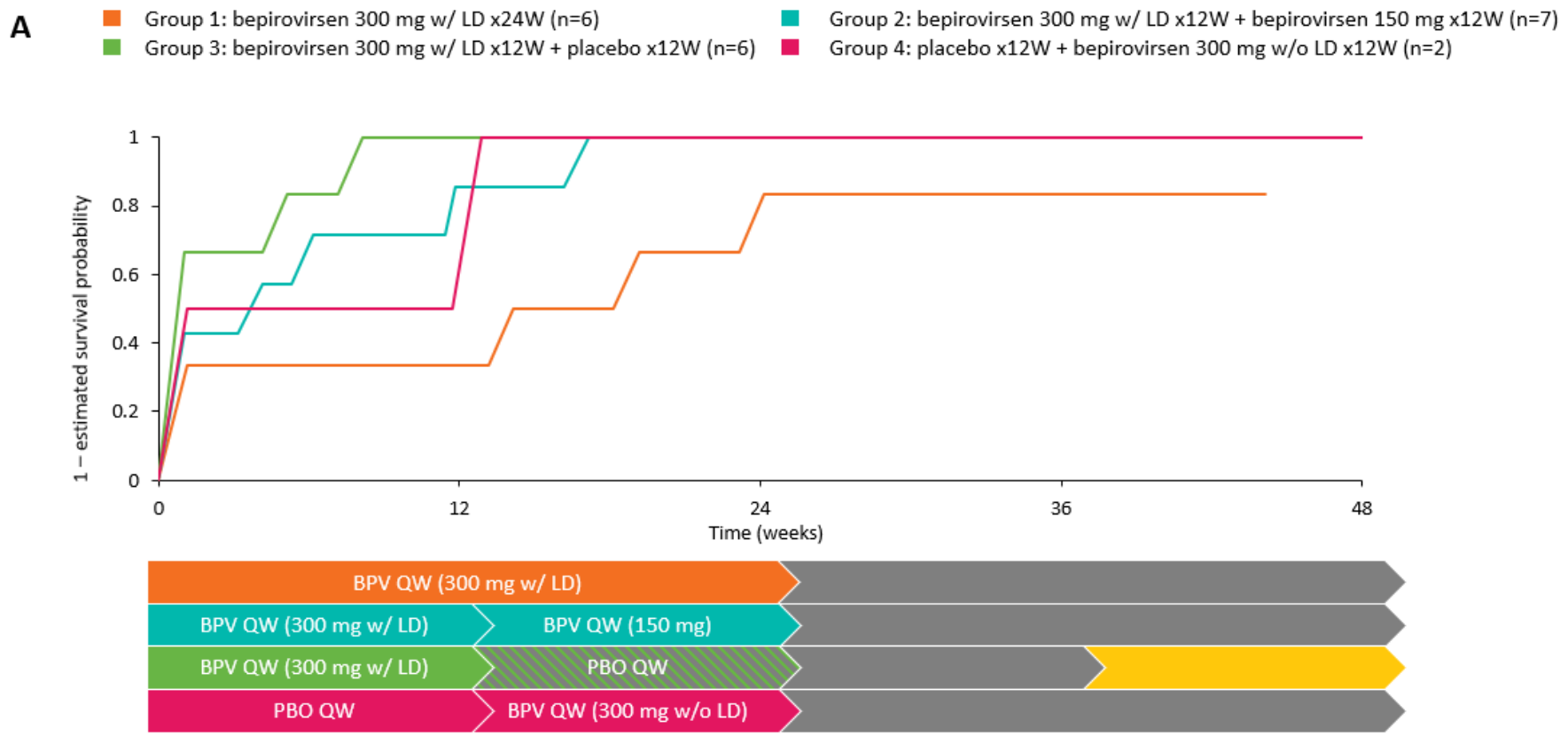
Figure S12. Categorical Changes from Baseline in HBV DNA in Participants Not Receiving NA Therapy (i.e., reductions of <1, ≥1–<2, ≥2–<3, ≥3 log10 IU/mL) (ITT Population).



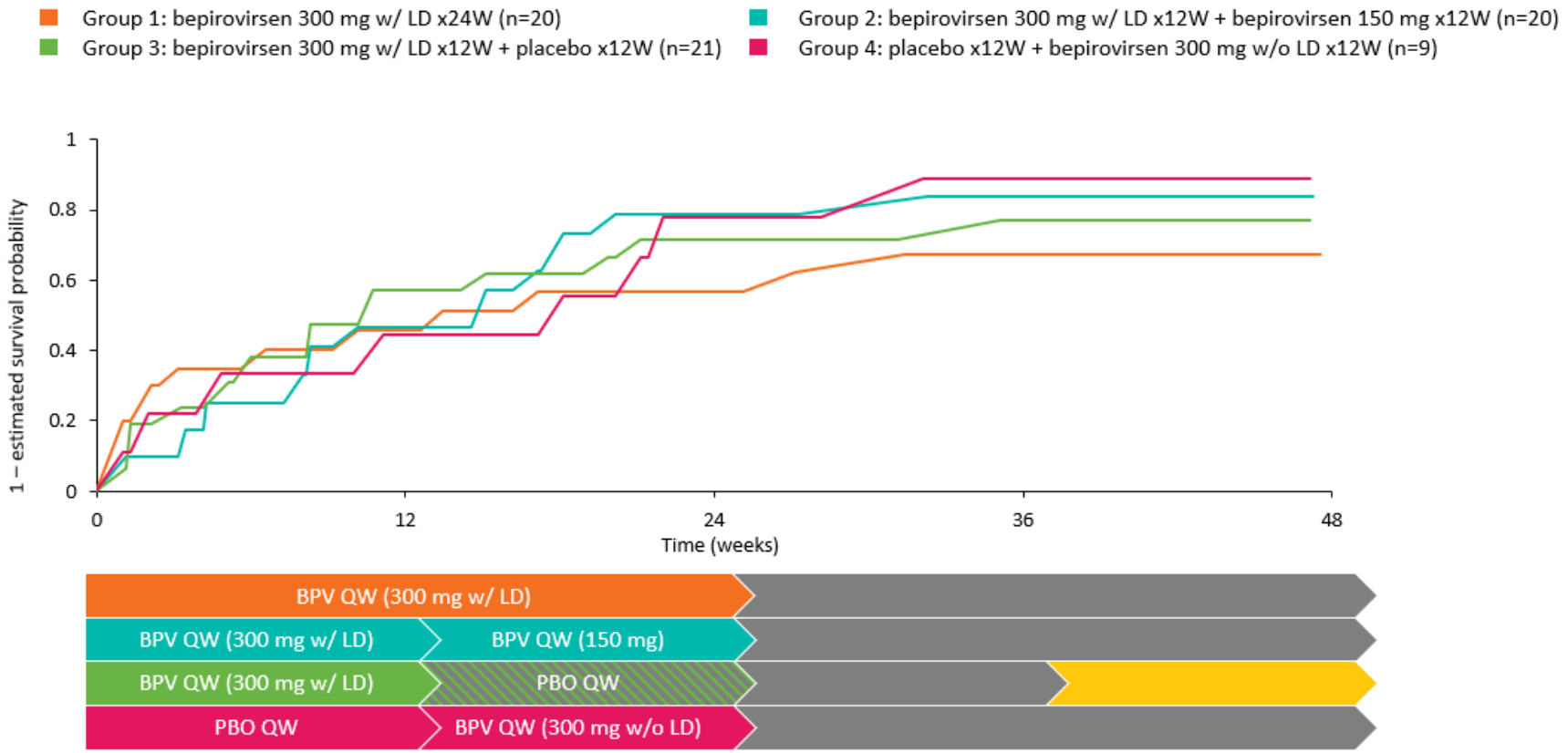
Percentages calculated based on the total number of participants in the ITT population.

DNA, deoxyribonucleic acid; HBV, hepatitis B virus; ITT, intent-to-treat; LD, loading dose; NA, nucleos(t)ide analogue; OT, off-treatment; QW, once a week; W, week; w/=with; w/o=without.

Figure S13. Time to ALT Normalization (ALT ≤ULN) in the Absence of Newly Initiated Antiviral Treatment in Participants with Baseline ALT >ULN (A) Receiving NA Therapy and (B) Not Receiving NA Therapy (ITT Population).



B



N numbers indicate the number of participants with ALT >ULN at baseline in each treatment group. Shaded gray arrows below the graphs indicate 24-week off-treatment follow-up; shaded yellow arrow below the graphs indicates additional off-treatment follow-up in Group 3. Panel A: Per protocol, participants receiving NA therapy were expected to continue their NA therapy throughout the study.

ALT, alanine aminotransferase; ITT, intent-to-treat; LD, loading dose; NA, nucleos(t)ide analogue; QW, once a week; ULN, upper limit of normal; W, week; w/=with; w/o=without.

Table S7. Full Eligibility Criteria.

Inclusion criteria

AGE
1. At least 18 years of age at the time of signing the informed consent [if country/site age requirements for consent differ, the more stringent (e.g., higher age) restriction will be required for that country/site].
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Participants who have documented chronic HBV infection ≥6 months prior to screening AND a. Not currently on nucleos(t)ide analogue therapy population defined as participants who never received HBV treatment (treatment naïve) OR must have ended nucleos(t)ide therapy at least 6 months prior to the screening visit OR b. Currently receiving stable nucleos(t)ide analogue therapy population defined as no changes to their nucleos(t)ide regimen from at least 6 months prior to screening and with no planned changes to the stable regimen over the duration of the study 3. Plasma or serum HBsAg concentration >100 IU/mL 4. Plasma or serum HBV DNA concentration a. Participants not currently on nucleos(t)ide analogue therapy, plasma or serum HBV DNA >2000 IU/mL b. Participants who are receiving stable nucleos(t)ide analogue therapy must be adequately suppressed, defined as plasma or serum HBV DNA <90 IU/mL 5. ALT a. ALT for treatment-naïve participants and for participants who are not currently receiving treatment i. ALT <3 X ULN (male: 40 IU/L, female: 33 IU/L) will be included initially

1. If agreed by the IDMC after review of safety data, the ALT inclusion criteria may be expanded to include participants with ALT <5 X ULN

b. ALT ≤2 X ULN for participants who are receiving stable nucleos(t)ide analogue therapy

SEX

6. Male and/or Female

a. A male participant is eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of study treatment

i. Refrain from donating sperm

ii. AND be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent OR must agree to use contraception/barrier as detailed below

1. Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

b. A female participant is eligible to participate:

i. If she is not pregnant or breastfeeding

ii. AND at least one of the following conditions applies:

1. Is not a WOCBP
2. OR is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency during the intervention period and for at least 90 days after the last dose of study treatment

iii. A WOCBP must have both

1. A confirmed menstrual period prior to the first dose of study intervention (additional evaluation [e.g., amenorrhea in athletes, birth control] should also be considered)
2. AND a negative highly sensitive pregnancy test (urine or serum) within 24 hours before the first dose of study treatment

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

INFORMED CONSENT

7. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.

Exclusion criteria

MEDICAL CONDITIONS
1. Clinically significant abnormalities, aside from chronic HBV infection in medical history (e.g., moderate-severe liver disease other than chronic HBV, acute coronary syndrome within 6 months of screening, major surgery within 3 months of screening, significant/unstable cardiac disease, uncontrolled diabetes, bleeding diathesis or coagulopathy) or physical examination 2. Co-infection with: a. Current or past history of HCV b. HIV c. HDV 3. History of or suspected liver cirrhosis and/or evidence of cirrhosis as determined by a. both APRI >2 and FibroSure/FibroTest result >0.7 i. If only one parameter (APRI or FibroSure/FibroTest) result is positive, a discussion with the Medical Monitor is required before inclusion in study is permitted b. Regardless of APRI of FibroSure/FibroTest score, if the participant meets one of the following historical criteria, they will be excluded from the study i. Liver biopsy (i.e., Metavir Score F4) ii. Liver stiffness >12 kPa 4. Diagnosed or suspected hepatocellular carcinoma as evidenced by the following a. Alpha-fetoprotein concentration ≥200 ng/mL

b. If the screening alpha fetoprotein concentration is ≥50 ng/mL and <200 ng/mL, the absence of liver mass must be documented by imaging within 6 months before randomization

5. History of malignancy within the past 5 years with the exception of specific cancers that are cured by surgical resection (e.g., skin cancer). Participants under evaluation for possible malignancy are not eligible.
6. History of vasculitis or presence of symptoms and signs of potential vasculitis (e.g., vasculitic rash, skin ulceration, repeated blood detected in urine without identified cause) or history/presence of other diseases that may be associated with vasculitis condition (e.g., systemic lupus erythematosus, rheumatoid arthritis, relapsing polychondritis, mononeuritis multiplex)
7. History of extrahepatic disorders possibly related to HBV immune conditions (e.g., nephrotic syndrome, any type of glomerulonephritis, polyarteritis nodosa, cryoglobulinemia, uncontrolled hypertension)
8. Positive (or borderline positive) ANCA at screening:
    a. Participants that meet this criterion may be considered for inclusion in the study following:
        i. Analysis of MPO-ANCA [pANCA] and PR3-ANCA [cANCA] AND
        ii. A discussion with the Medical Monitor to review participant's complete medical history to ensure no past history or current manifestations of a vasculitic/inflammatory/auto-immune condition
9. Low C3 at screening AND evidence of past history or current manifestations of vasculitic/inflammatory/auto-immune conditions

a. All participants with low C3 at screening should have their medical history discussed with the Medical Monitor prior to enrollment

10. History of alcohol or drug abuse/dependence

    a. Current alcohol use as judged by investigator to potentially interfere with participant compliance

    b. History of or current drug abuse/dependence as judged by the investigator to potentially interfere with participant compliance

        i. Refers to illicit drugs and substances with abuse potential. Medications that are used by the participant as directed, whether over-the-counter or through prescription, are acceptable and would not meet the exclusion criteria

PRIOR/CONCOMITANT THERAPY

11. Currently taking, or took within 3 months of screening, any immunosuppressing drugs (e.g., prednisone), other than a short course of therapy (≤2 weeks) or topical/inhaled steroid use

12. Participants for whom immunosuppressive treatment is not advised, including therapeutic doses of steroids

13. Currently taking, or took within 12 months of screening, any interferon-containing therapy

14. Participants requiring anti-coagulation therapies (e.g., warfarin, Factor Xa inhibitors or anti-platelet agents like clopidogrel)

15. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 5 half-lives (if known) or twice the duration (if known) of the biological effect of the study treatment (whichever is longer) or 90 days (if half-life or duration is unknown)

16. Prior treatment with any oligonucleotide or siRNA within 12 months prior to the first dosing day

DIAGNOSTIC ASSESSMENTS

17. Fridericia's QT correction formula (QTcF) ≥450 msec (if single electrocardiogram [ECG] at screening shows QTcF ≥450 msec, a mean of triplicate measurements should be used to confirm that participant meets exclusion criterion)

18. Laboratory results as follows

    a. Serum albumin <3.5 g/dL

    b. Glomerular filtration rate (GFR) <60 mL/min /1.73m^2 as calculated by the CKD-EPI formula (for Japan, JSN-CKDI equation)

    c. INR >1.25

    d. Platelet count <140 X 109/L

    e. Total bilirubin >1.25 x ULN

        i. For participants with benign unconjugated hyperbilirubinemia with total bilirubin >1.25 x ULN, discussion for inclusion to the study is required with the Medical Monitor

    f. Urine ACR ≥0.03 mg/mg (or ≥30 mg/g). In the event of an ACR above this threshold, eligibility may be confirmed by a second measurement

        i. In cases where participants have low urine albumin and low urine creatinine levels resulting in a urine ACR calculation ≥0.03 mg/mg (or ≥30 mg/g), the investigator should confirm that the participant does not have a history of diabetes, hypertension or other risk factors that may affect renal function and discuss with the Medical Monitor, or designee

OTHER EXCLUSIONS
19. History of/sensitivity to bepirovirsen or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation

ACR, albumin to creatinine ratio; ALT, alanine aminotransferase; ANCA, antineutrophil cytoplasmic antibody; APRI, aspartate aminotransferase (AST)-platelet ratio index; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; ICF, informed consent form; IDMC, independent data monitoring committee; INR, international normalized ratio; JSN-CKDI, Japan Society of Nephrology Chronic Kidney Disease Initiative; QTcF, QT correction formula; ULN, upper limit of normal; WOCBP, woman of childbearing potential.

Table S8. Primary Outcome and Other Estimands.

	Estimand
Primary outcome	The primary estimand for each population (participants receiving NA therapy and participants not receiving NA therapy) is the proportion of participants in each treatment Group 1, 2, and 3 who achieve HBsAg <LLOD and HBV DNA <LLOQ for 24 weeks after the planned end of bepirovirsen treatment in the absence of newly initiated antiviral treatment, regardless of completing treatment, interruptions in treatment or adherence to treatment had they not been affected by wide disruptive events. A single value HBsAg ≥LLOD or HBV DNA ≥LLOQ between end of bepirovirsen treatment and 24 weeks after the planned end of bepirovirsen treatment was classed as a failure. **Intercurrent events**: use of any medication for the purpose of suppressing HBV replication, and discontinuation of/interruption of/adherence to treatment. The use of medication for the purpose of suppressing HBV replication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to treatment will be ignored (treatment policy). Wide disruptive events (such as the COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to treatment will be handled assuming they had not happened (hypothetical strategy).
Modified primary outcome	This additional estimand is defined in the same way as the primary estimand, except the variable is defined using a modified definition of the primary outcome, defined as HBsAg <LLOD and HBV DNA <LLOQ for 24 weeks after the planned end of bepirovirsen treatment in the absence of newly initiated antiviral treatment. Any observation of HBsAg ≥LLOD or HBV DNA ≥LLOQ must be confirmed at a consecutive visit (including unscheduled visits) for the participant to be classed as having lost their response. Participants who have a value of HBsAg ≥LLOD or HBV DNA ≥LLOQ at their last visit, which cannot be confirmed due to no further follow-up, will be treated as non-responders.

	It is the proportion of participants in each treatment Group 1, 2, 3 and 4 who achieve the modified definition of the primary outcome for 24 weeks after the planned end of bepirovirsen treatment in the absence of antiviral treatment, regardless of completing treatment, interruptions in treatment or adherence to treatment, had they not been affected by wide disruptive events.
Hypothetical strategy	This additional estimand is defined in the same way as the primary estimand, except the intercurrent event of discontinuation of, interruption of, and adherence to treatment will be handled assuming they had not happened (hypothetical strategy). It is the proportion of participants in each treatment Group 1, 2, 3 and 4 for each population (participants receiving NA therapy and participants not receiving NA therapy) who achieve the primary endpoint sustained for 24 weeks after the planned end of bepirovirsen treatment in the absence of antiviral treatment, had they not been affected by discontinuation of treatment, interruptions in treatment, adherence to treatment, or wide disruptive events.
Actual end of treatment	This additional estimand is defined in the same way as the primary estimand, except the assessment time frame for participants achieving the primary outcome will be 24 weeks after the actual end of treatment. Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. It is the proportion of participants in each treatment Group 1, 2, 3 and 4 for each population (participants receiving NA therapy and participants not receiving NA therapy) who achieve the primary outcome sustained for 24 weeks after the actual end of bepirovirsen treatment in the absence of antiviral treatment, regardless of completing treatment, interruptions in treatment or adherence to treatment, had they not been affected by wide disruptive events.
Principal stratum strategy	This additional estimand is defined in the same way as the primary estimand, except for the population, variable and intercurrent events definitions. The population is participants not receiving NA therapy. The variable for this estimand will be defined as HBsAg

	<LLOD and HBV DNA <LLOQ sustained for 24 weeks after the planned end of bepirovirsen treatment in the absence of antiviral treatment for medical reasons. The intercurrent event of use of rescue medication will be separated into two: 1. Use of antiviral treatment for medical reasons 2. Use of antiviral treatment because of a protocol deviation The use of antiviral treatment for medical reasons has been incorporated into the definition of variable (composite strategy). The use of antiviral treatment because of a protocol deviation will be handled by excluding these participants from the analysis (principal stratum strategy). It is the proportion of participants not receiving NA therapy in each treatment Group 1, 2, 3 and 4 who achieve the primary outcome sustained for 24 weeks after the planned end of bepirovirsen treatment in the stratum of participants who did not use antiviral treatment in error, in the absence of antiviral treatment for medical reasons, regardless of completing treatment, interruptions in treatment or adherence to treatment, had they not been affected by wide disruptive events.

DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOD, lower limit of detection; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue.

Table S9. MedDRA SMQs, HLT or Individual PTs Used to Define the Adverse Events of Special Interest.

AESI	Group of terms (MedDRA SMQ, HLT or individual PTs)	Comment
Injection site reactions	• PTs: ○ Injection site urticaria ○ Injection site thrombosis ○ Injection site extravasation ○ Injection site erosion ○ Injection site erythema ○ Injection site granuloma ○ Injection site induration ○ Injection site inflammation ○ Injection site irritation ○ Injection site mass ○ Injection site necrosis ○ Injection site nodule ○ Injection site edema ○ Injection site pain ○ Injection site swelling ○ Injection site ulcer ○ Injection site bruising ○ Injection site hematoma ○ Injection site hemorrhage ○ Immediate post-injection reaction ○ Injection related reaction ○ Injection site dermatitis ○ Injection site eczema ○ Injection site hypersensitivity ○ Injection site rash ○ Injection site recall reaction ○ Injection site vasculitis	

AESI	Group of terms (MedDRA SMQ, HLT or individual PTs)	Comment
	○ Injection site panniculitis ○ Injection site phlebitis ○ Injection site pruritus ○ Injection site abscess ○ Injection site anesthesia ○ Injection site cellulitis ○ Injection site discoloration ○ Injection site discomfort ○ Injection site warmth	
Vascular inflammation and complement activation	• Vasculitis SMQ (Broad) • Hypersensitivity SMQ (Broad) • Immune response protein analyses NEC (HLT) • PTs: ○ Blood creatine increased ○ Blood creatinine abnormal ○ Blood urea abnormal ○ Blood urea increased ○ Blood urine ○ Blood urine present ○ Body temperature increased ○ C-reactive protein abnormal ○ C-reactive protein increased ○ Creatinine renal clearance abnormal ○ Creatinine renal clearance decreased ○ Glomerular filtration rate abnormal ○ Glomerular filtration rate decreased ○ Glomerulonephritis ○ Hematuria ○ Headache ○ Influenza	

AESI	Group of terms (MedDRA SMQ, HLT or individual PTs)	Comment
	○ Influenza like illness ○ Injection site pruritis ○ Injection site reaction ○ Injection site swelling ○ Myalgia ○ Protein urine present ○ Proteinuria ○ Pyrexia ○ Renal function test abnormal ○ Renal impairment ○ Urine albumin creatinine ratio abnormal ○ Urine albumin/creatinine ratio increased	
Thrombocytopenia	• Hematopoietic thrombocytopenia SMQ (broad) • Hemorrhage terms (excluding laboratory terms) SMQ)	Hematopoietic thrombocytopenia is a sub SMQ of hematopoietic cytopenias SMQ Hemorrhage terms (excluding laboratory terms) SMQ is a sub SMQ of hemorrhages SMQ
ALT increase	• Drug related hepatic disorders – comprehensive search (SMQ) (Broad)	Drug-related hepatic disorders is a sub SMQ of hepatic disorders SMQ
Renal injury	• Acute renal failure SMQ (Broad) • PTs: ○ Blood urine ○ Blood urine present ○ Glomerulonephritis ○ Hematuria	Nephropathy toxic is PT captured in this SMQ, LLT is drug-induced kidney injury

AESI	Group of terms (MedDRA SMQ, HLT or individual PTs)	Comment
	○ Urine albumin creatinine ratio abnormal ○ Urine albumin/creatinine ratio increase	

HLT, High Level Term; LLT, Lowest Level Term; MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; PT, Preferred Term; SMQ, Standardized MedDRA Query.

Table S10. Representativeness of Study Participants.

Category	Example
Disease, problem, or condition under investigation	Chronic HBV infection
Special considerations related to:	
Sex and gender	The prevalence of HBV infection is higher among men than women. In 2019, 17,151 cases of hepatitis B were reported in males (8.8 cases per 100,000 population) and 11,914 cases in females (5.8 cases per 100,000 population) in Europe.[1]
Age	Most people currently living with HBV were infected as infants before vaccination was available.[2] In 2019 in Europe, just below one-third of all cases (28%) were in the 25–34 years age group; the same age category reported the highest rate of chronic infections.[1] The next most prevalent group being people 35–44 years of age.[1] In 2013 across four states (Florida, Massachusetts, Michigan, and Washington), two cities (Philadelphia and San Francisco), and 57 counties in New York State, 947 (34.4%) of HBV infection were in the 25−39 years age group and 855 (31.0%) cases in the 40–54 years age group.[3]
Race or ethnic group	In 2013, non-Hispanic Asians were estimated to account for 53.5% of all chronic HBV infections in the US.[3]
Geography	Prevalence is highest in WHO Western Pacific and African regions.[2] In 2016, the prevalence of HBsAg positive infections, which are indicative of HBV historical prevalence, was highest in the WHO African Region.[4] In 2016, China accounted for approximately one-third (86 million) of people living with hepatitis B.[4]

Other considerations	The population of people living with HBV infection is clinically diverse with different prognosis in the respective subgroups including patients with active liver inflammation (chronic hepatitis B) and those without (chronic HBV infection), patients with and without cirrhosis, and patients with co-infections such as HCV, HDV, and HIV.[5] Left untreated, 20% or more of patients with viral hepatitis will die from chronic liver disease, mainly cirrhosis and HCC – resulting in an HBV-associated annual death toll approaching 900,000.[2] Currently, functional cure which is accepted as the optimal endpoint of HBV treatment, is rare with current standard of care (<5%).[6,7]
Overall representativeness of this trial	In this study, the majority (73% participants receiving NA therapy; 54% participants not receiving NA therapy) of participants were males, which is representative of chronic HBV population that shows a higher ratio of men to women. In line with the ethnic prevalence in the chronic HBV population, most participants were Asian (52% participants receiving NA therapy; 57% participants not receiving NA therapy) and non-Hispanic (96% participants receiving NA therapy; 96% participants not receiving NA therapy). The age of participants in this trial was representative of people living with HBV, with a mean age of 48 years for participants receiving NA therapy and 43 years for participants not receiving NA therapy, and most participants (57% receiving NA therapy and 72% not receiving NA therapy) were <50 years of age. People living with HBV co-infected with HCV, HDV, or HIV were excluded from this study. However, the prevalence of these populations is low.

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; NA, nucleos(t)ide analogue; WHO, World Health Organization.

Methods: Background information on the sex and gender, age, race or ethnicity, and geography of the broader population affected by chronic hepatitis B virus infection was extracted from published data, and data from health organizations such as the European Centre for Disease Prevention and Control, the World Health Organization and the Center for Disease control and Prevention. The information and interpretation were reviewed by the authors.

References

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Table S11. Proportion of Participants Achieving HBsAg and HBV DNA Loss for 24 Weeks After Treatment End Using the Primary Outcome and Other Estimands (ITT Population).

	Participants Receiving NA Therapy				**Participants Not Receiving NA Therapy**			
	Group 1 bepirovirsen 300 mg w/LD x24W N=68	**Group 2 bepirovirsen 300 mg w/LD x12W + bepirovirsen 150 mg x12W N=68**	**Group 3 bepirovirsen 300 mg w/LD x12W + placebo x12W N=68**	**Group 4 placebo x12W + bepirovirsen 300 mg w/o LD x12W N=23**	**Group 1 bepirovirsen 300 mg w/LD x24W N=70**	**Group 2 bepirovirsen 300 mg w/LD x12W + bepirovirsen 150 mg x12W N=68**	**Group 3 bepirovirsen 300 mg w/LD x12W + placebo x12W N=68**	**Group 4 placebo x12W + bepirovirsen 300 mg w/o LD x12W N=24**
Primary outcome estimand								
HBsAg and HBV DNA loss, n (%)	6 (9)	6 (9)	2 (3)	0	7 (10)	4 (6)	1 (1)	0
Point estimate of response rate, % (95% CrI)	9 (0, 31)	9 (0, 43)	3 (0, 16)	2 (0, 8)*	10 (0, 38)	6 (0, 25)	2 (0, 6)*	2 (0, 8)*
Modified primary outcome estimand								

HBsAg and HBV DNA loss, n (%)	7 (10)	6 (9)	3 (4)	0	10 (14)	4 (6)	1 (1)	1 (4)
Point estimate of response rate, % (95% CrI)	11 (0, 36)	9 (0, 43)	4 (0, 22)	2 (0, 8)*	15 (0, 64)	6 (0, 25)	2 (0, 6)*	4 (0, 33)
Hypothetical strategy estimand								
HBsAg and HBV DNA loss, n (%)	4 (6)	6 (9)	2 (3)	0	4 (6)	2 (3)	1 (1)	0
Point estimate of response rate, % (95% CrI)	7 (0, 35)	10 (0, 51)	3 (0, 18)	2 (0, 9)*	8 (0, 41)	3 (0, 16)	2 (0, 7)*	2 (0, 9)*
Actual end of treatment estimand								
HBsAg and HBV DNA loss, n (%)	6 (9)	6 (9)	2 (3)	0	7 (10)	4 (6)	0	0
Point estimate of response rate, % (95% CrI)	9 (0, 31)	9 (0, 43)	3 (0, 16)	2 (0, 8)*	10 (0, 38)	6 (0, 25)	2 (0, 6)*	2 (0, 8)*
Principle stratum strategy estimand†								
HBsAg and HBV DNA loss, n (%)	-	-	-	-	7 (10)	4 (6)	1 (2)	0

Point estimate of response rate, % (95% CrI)	-	-	-	-	10 (0, 38)	6 (0, 28)	2 (0, 6)*	2 (0, 8)*

*Point estimates and credible intervals from post-hoc unstratified Bayesian analysis due to non-convergence of the pre-specified stratified Bayesian hierarchical model – additional details are available in **Supplementary methods**; †Participants not receiving NA therapy: n=66 in Group 2 and Group 3, n=22 in Group 4.

CrI, credible interval; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ITT, intent-to-treat; LD, loading dose; LLOQ, lower limit of quantitation; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Table S12. ALT Normalization in the Absence of Rescue Medication (ITT Population).

	Participants Receiving NA Therapy				**Participants Not Receiving NA Therapy**			
	Group 1 bepirovirsen 300 mg w/LD x24W N=68	**Group 2 bepirovirsen 300 mg w/LD x12W + bepirovirsen 150 mg x12W N=68**	**Group 3 bepirovirsen 300 mg w/LD x12W + placebo x12W N=68**	**Group 4 placebo x12W + bepirovirsen 300 mg w/o LD x12W N=23**	**Group 1 bepirovirsen 300 mg w/LD x24W N=70**	**Group 2 bepirovirsen 300 mg w/LD x12W + bepirovirsen 150 mg x12W N=68**	**Group 3 bepirovirsen 300 mg w/LD x12W + placebo x12W N=68**	**Group 4 placebo x12W + bepirovirsen 300 mg w/o LD x12W N=24**
ALT >ULN at baseline, n (%)	6 (9)	7 (10)	6 (9)	2 (9)	20 (29)	20 (29)	21 (31)	9 (38)
Participants with ALT normalization at EoT*, % (95% CI)	67 (19, 90)	100 (NE, NE)	100 (NE, NE)	100 (NE, NE)	57 (33, 75)	79 (54, 91)	57 (34, 75)	78 (36, 94)
Participants with ALT normalization at 24 weeks post EoT*, % (95% CI)	NE (NE, NE)	100 (NE, NE)	100 (NE, NE)	100 (NE, NE)	68 (43, 83)	84 (59, 94)	77 (53, 90)	89 (43, 98)

Estimated median (95% CI) time to ALT normalization (weeks)	16.6 (1.1, NE)	4.1 (1.0, 11.9)	1.0 (1.0, 8.1)	7.0 (1.1, NE)	13.4 (2.1, NE)	15.1 (4.3, 18.1)	10.7 (5.1, 21.1)	18.1 (1.0, 32.1)

*EoT is Week 12 for Group 3 and Week 24 for Groups 1, 2, and 4.

ALT, alanine aminotransferase; CI, confidence interval; EoT, end of treatment; ITT, intent-to-treat; LD, loading dose; NA, nucleos(t)ide analogue; NE, not estimated; ULN, upper limit of normal; W, week; w/=with; w/o=without.

Table S13. Adverse Events That Occurred in ≥5% of Participants Receiving NA Therapy in Week 1–12 (Safety Population).

Adverse event by Preferred Term, n (%)	**Group 1** **bepirovirsen** **300 mg w/LD x24W** **N=68**	**Group 2** **bepirovirsen** **300 mg w/LD x12W + bepirovirsen 150 mg x12W** **N=67**	**Group 3** **bepirovirsen** **300 mg w/LD x12W + placebo x12W** **N=68**	**Group 4** **placebo x12W + bepirovirsen** **300 mg w/o LD x12W** **N=23**	**Total** **N=226**
Injection-site erythema	31 (46)	37 (55)	33 (49)	1 (4)	102 (45)
Injection-site pain	8 (12)	14 (21)	21 (31)	1 (4)	44 (19)
Injection-site pruritus	11 (16)	15 (22)	15 (22)	0	41 (18)
Injection-site discoloration	4 (6)	9 (13)	12 (18)	0	25 (11)
Pyrexia	8 (12)	4 (6)	8 (12)	0	20 (9)
Injection-site bruising	6 (9)	6 (9)	7 (10)	2 (9)	21 (9)

Injection-site swelling	4 (6)	4 (6)	13 (19)	0	21 (9)
Injection-site discomfort	2 (3)	9 (13)	9 (13)	0	20 (9)
Alanine aminotransferase increased	7 (10)	8 (12)	4 (6)	0	19 (8)
Headache	3 (4)	5 (7)	5 (7)	1 (4)	14 (6)
Fatigue	4 (6)	2 (3)	6 (9)	0	12 (5)
Myalgia	5 (7)	2 (3)	4 (6)	0	11 (5)

LD, loading dose; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Table S14. Adverse Events That Occurred in ≥5% of Participants Not Receiving NA Therapy in Week 1–12 (Safety Population).

Adverse event by Preferred Term, n (%)	**Group 1** **bepirovirsen 300 mg w/LD x24W** **N=70**	**Group 2** **bepirovirsen 300 mg w/LD x12W + bepirovirsen 150 mg x12W** **N=67**	**Group 3** **bepirovirsen 300 mg w/LD x12W + placebo x12W** **N=68**	**Group 4** **placebo x12W + bepirovirsen 300 mg w/o LD x12W** **N=24**	**Total** **N=229**
Injection-site erythema	33 (47)	29 (43)	36 (53)	0	98 (43)
Injection-site pruritus	19 (27)	14 (21)	17 (25)	1 (4)	51 (22)
Injection-site pain	19 (27)	11 (16)	14 (21)	1 (4)	45 (20)
Pyrexia	10 (14)	15 (22)	14 (21)	0	39 (17)
Headache	10 (14)	11 (16)	13 (19)	2 (8)	36 (16)
Injection-site bruising	11 (16)	8 (12)	12 (18)	3 (13)	34 (15)

Alanine aminotransferase increased	13 (19)	9 (13)	8 (12)	1 (4)	31 (14)
Fatigue	13 (19)	7 (10)	5 (7)	0	25 (11)
Injection-site swelling	10 (14)	5 (7)	5 (7)	0	20 (9)
Injection-site discoloration	6 (9)	5 (7)	5 (7)	0	16 (7)
Complement factor C3 decreased	6 (9)	3 (4)	6 (9)	1 (4)	16 (7)
Aspartate aminotransferase increased	5 (7)	4 (6)	5 (7)	1 (4)	15 (7)
Injection-site induration	6 (9)	5 (7)	2 (3)	0	13 (6)
Injection-site discomfort	3 (4)	5 (7)	4 (6)	0	12 (5)
Complement factor C4 decreased	4 (6)	4 (6)	4 (6)	0	12 (5)
Myalgia	7 (10)	4 (6)	0	1 (4)	12 (5)
Back pain	4 (6)	3 (4)	2 (3)	2 (8)	11 (5)

LD, loading dose; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Table S15. Adverse Events and Serious Adverse Events by Visit Week in Participants Receiving NA Therapy (Safety Population).

	Group 1 **bepirovirsen 300 mg w/LD x24W** **N=68**	**Group 2** **bepirovirsen 300 mg w/LD x12W + bepirovirsen 150 mg x12W** **N=67**	**Group 3** **bepirovirsen 300 mg w/LD x12W + placebo x12W** **N=68**	**Group 4** **placebo x12W + bepirovirsen 300 mg w/o LD x12W** **N=23**
Adverse events, n (%)				
All visits	56 (82)	59 (88)	53 (78)	16 (70)
Week 1–12	53 (78)	57 (85)	52 (76)	10 (43)
Week 13–24	34 (50)	31 (46)	26 (38)	15 (65)
Week 25–48	21 (31)	21 (31)	22 (32)	6 (26)
Serious adverse events, n (%)				
All visits	1 (1)	1 (1)	4 (6)	0

Week 1–12	1 (1)	1 (1)	3 (4)	0
Week 13–24	0	0	0	0
Week 25–48	0	0	1 (1)	0

LD, loading dose; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Table S16. Adverse Events and Serious Adverse Events by Visit Week in Participants Not Receiving NA Therapy (Safety Population).

	Group 1 **bepirovirsen 300 mg w/LD x24W** **N=70**	**Group 2** **bepirovirsen 300 mg w/LD x12W + bepirovirsen 150 mg x12W** **N=67**	**Group 3** **bepirovirsen 300 mg w/LD x12W + placebo x12W** **N=68**	**Group 4** **placebo x12W + bepirovirsen 300 mg w/o LD x12W** **N=24**
Adverse events, n (%)				
All visits	65 (93)	60 (90)	62 (91)	19 (79)
Week 1–12	63 (90)	55 (82)	59 (87)	13 (54)
Week 13–24	47 (67)	40 (60)	40 (59)	18 (75)
Week 25–48	27 (39)	34 (51)	29 (43)	7 (29)
Serious adverse events, n (%)				
All visits	6 (9)	2 (3)	3 (4)	0

Week 1–12	3 (4)	0	0	0
Week 13–24	3 (4)	2 (3)	2 (3)	0
Week 25–48	0	0	1 (1)	0

LD, loading dose; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Table S17. Adverse Events That Occurred in ≥5% of Participants Receiving NA Therapy (Safety Population).

Adverse event by Preferred Term, n (%)	**Group 1** **bepirovirsen** **300 mg w/LD x24W** **N=68**	**Group 2** **bepirovirsen** **300 mg w/LD x12W + bepirovirsen 150 mg x12W** **N=67**	**Group 3** **bepirovirsen** **300 mg w/LD x12W + placebo x12W** **N=68**	**Group 4** **placebo x12W + bepirovirsen** **300 mg w/o LD x12W** **N=23**	**Total** **N=226**
Injection-site erythema	36 (53)	37 (55)	34 (50)	5 (22)	112 (50)
Injection-site pain	11 (16)	15 (22)	21 (31)	6 (26)	53 (23)
Injection-site pruritus	14 (21)	17 (25)	15 (22)	2 (9)	48 (21)
Injection-site discoloration	8 (12)	9 (13)	14 (21)	2 (9)	33 (15)
Pyrexia	10 (15)	6 (9)	10 (15)	6 (26)	32 (14)
Injection-site bruising	7 (10)	11 (16)	7 (10)	4 (17)	29 (13)

Injection-site swelling	4 (6)	4 (6)	13 (19)	1 (4)	22 (10)
Injection-site discomfort	2 (3)	9 (13)	9 (13)	1 (4)	21 (9)
Fatigue	5 (7)	4 (6)	7 (10)	1 (4)	17 (8)
Alanine aminotransferase increased	7 (10)	8 (12)	4 (6)	5 (22)	24 (11)
Headache	5 (7)	6 (9)	8 (12)	3 (13)	22 (10)
COVID-19	2 (3)	8 (12)	5 (7)	1 (4)	16 (7)
Back pain	4 (6)	5 (7)	6 (9)	0	15 (7)
Arthralgia	3 (4)	3 (4)	6 (9)	1 (4)	13 (6)
Myalgia	5 (7)	2 (3)	4 (6)	0	11 (5)
Nasopharyngitis	1 (1)	1 (1)	5 (7)	4 (17)	11 (5)

LD, loading dose; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Table S18. Adverse Events That Occurred in ≥5% of Participants Not Receiving NA Therapy (Safety Population).

Adverse event by Preferred Term, n (%)	**Group 1** **bepirovirsen 300 mg w/LD x24W** **N=70**	**Group 2** **bepirovirsen 300 mg w/LD x12W + bepirovirsen 150 mg x12W** **N=67**	**Group 3** **bepirovirsen 300 mg w/LD x12W + placebo x12W** **N=68**	**Group 4** **placebo x12W + bepirovirsen 300 mg w/o LD x12W** **N=24**	**Total** **N=229**
Injection-site erythema	34 (49)	30 (45)	37 (54)	10 (42)	111 (48)
Injection-site pruritus	23 (33)	16 (24)	19 (28)	2 (8)	60 (26)
Injection-site pain	20 (29)	13 (19)	14 (21)	6 (25)	53 (23)
Pyrexia	15 (21)	17 (25)	17 (25)	4 (17)	53 (23)
Alanine aminotransferase increased	17 (24)	15 (22)	12 (18)	4 (17)	48 (21)
Headache	14 (20)	14 (21)	14 (21)	4 (17)	46 (20)

Injection-site bruising	13 (19)	10 (15)	14 (21)	4 (17)	41 (18)
Injection-site discoloration	13 (19)	11 (16)	6 (9)	2 (8)	32 (14)
Fatigue	13 (19)	7 (10)	8 (12)	0	28 (12)
Aspartate aminotransferase increased	8 (11)	9 (13)	7 (10)	2 (8)	26 (11)
Injection-site swelling	10 (14)	7 (10)	5 (7)	0	22 (10)
Myalgia	10 (14)	7 (10)	2 (3)	3 (13)	22 (10)
Complement factor C3 decreased	7 (10)	4 (6)	6 (9)	4 (17)	21 (9)
Complement factor C4 decreased	5 (7)	4 (6)	4 (6)	3 (13)	16 (7)
Injection-site discomfort	4 (6)	6 (9)	4 (6)	2 (8)	16 (7)
Injection-site induration	6 (9)	7 (10)	2 (3)	1 (4)	16 (7)
Injection-site hematoma	8 (11)	4 (6)	2 (3)	1 (4)	15 (7)

Platelet count decreased	8 (11)	3 (4)	3 (4)	0	14 (6)
COVID-19	3 (4)	6 (9)	4 (6)	1 (4)	14 (6)
Rash	1 (1)	7 (10)	5 (7)	1 (4)	14 (6)
Pruritus	5 (7)	4 (6)	3 (4)	1 (4)	13 (6)
Nausea	7 (10)	4 (6)	2 (3)	0	13 (6)
Back pain	4 (6)	4 (6)	3 (4)	2 (8)	13 (6)
Asthenia	3 (4)	1 (1)	7 (10)	0	11 (5)
Complement factor increased	6 (9)	1 (1)	4 (6)	0	11 (5)
Nasopharyngitis	4 (6)	2 (3)	4 (6)	1 (4)	11 (5)

LD, loading dose; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Table S19. Serious Adverse Events in Participants Receiving NA Therapy (Safety Population).

Serious adverse event by Preferred Term, n (%)	**Group 1** **bepirovirsen** **300 mg w/LD x24W** **N=68**	**Group 2** **bepirovirsen** **300 mg w/LD x12W + bepirovirsen 150 mg x12W** **N=67**	**Group 3** **bepirovirsen** **300 mg w/LD x12W + placebo x12W** **N=68**	**Group 4** **placebo x12W + bepirovirsen** **300 mg w/o LD x12W** **N=23**
Cryoglobulinemia	1 (1)*	0	0	0
Muscle injury	0	1 (1)	0	0
Hypotension	0	0	1 (1)	0
Hemorrhoids	0	0	1 (1)	0
Cerebral infarction	0	0	1 (1)	0
Interstitial lung disease†	0	0	1 (1)	0

*Considered related to treatment in the opinion of the investigator; †Covid-19 pneumonia.

LD, loading dose; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.

Table S20. Serious Adverse Events in Participants Not Receiving NA Therapy (Safety Population).

Serious adverse event by Preferred Term, n (%)	**Group 1** **bepirovirsen** **300 mg w/LD x24W** **N=70**	**Group 2** **bepirovirsen** **300 mg w/LD x12W + bepirovirsen 150 mg x12W** **N=67**	**Group 3** **bepirovirsen** **300 mg w/LD x12W + placebo x12W** **N=68**	**Group 4** **placebo x12W + bepirovirsen** **300 mg w/o LD x12W** **N=24**
Bile duct cancer	1 (1)	0	0	0
Chest pain	1 (1)	0	0	0
Systemic inflammatory response syndrome	1 (1)*	0	0	0
Hepatitis B	1 (1)*	0	0	0
Lymphadenopathy	1 (1)	0	0	0
Hepatic function abnormal	1 (1)*	0	0	0
COVID-19 pneumonia	0	1 (1)	0	0

Spinal column injury	0	1 (1)	0	0
Hepatocellular carcinoma	0	0	1 (1)	0
Invasive ductal breast carcinoma	0	0	1 (1)	0
Concussion	0	0	1 (1)	0
Cervical dysplasia	0	0	1 (1)	0

*Considered related to treatment in the opinion of the investigator.

LD, loading dose; NA, nucleos(t)ide analogue; W, week; w/=with; w/o=without.