Supplementary Appendix

Supplement to: Hou J, Lim S-G, Buti M, et al. Phase 3 results of bepirovirsen treatment for chronic hepatitis B virus infection. N Engl J Med. DOI: 10.1056/NEJMoa2515131

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

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B-Well Study Group: investigators and study sites*

*Investigators from study enrollment to the primary endpoint data cut date are listed alphabetically by country/region and last name. Sites without enrollment are not listed.

†This investigator has passed away; we gratefully acknowledge their contributions to the studies.

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Trial registration

B-Well 1 and 2 are registered with ClinicalTrials.gov (NCT05630807 [https://clinicaltrials.gov/study/NCT05630807] and NCT05630820 [https://clinicaltrials.gov/study/NCT05630820], respectively). B-Well 1 and 2 are identical in study design for replication purposes as required by some regulatory agencies, with the exception of an optional exit interview in B-Well 1, which is not reported in this manuscript.

Supplementary Methods

Enrollment, randomization, and blinding

All participants were centrally randomized using Interactive Response Technology, stratified by screening HBsAg levels >100 to ≤1000 IU/mL or >1000 to ≤3000 IU/mL. Investigators/site staff, participants, and the sponsor were blinded to each participant's assigned study intervention throughout the course of the study. Study intervention was dispensed at the study visits and administered by the investigator or suitably trained designee. Study treatment and placebo were administered by subcutaneous injection using syringes selected to minimize any difference in injection force and masked for color. Unblinded monitors were permitted access to unblinded study intervention records at the investigative sites to verify that randomization and dispensing were performed accurately.

Assays used to assess virology markers

HBsAg

At screening and for monitoring, HBsAg was assessed quantitatively using the Elecsys HBsAg II quant II assay (Roche), with a limit of detection of 0.05 IU/mL. For assessing eligibility to stop NA treatment and for the primary endpoint analysis, HBsAg was assessed qualitatively using the Elecsys HBsAg II assay (Roche), with a limit of detection of less than 0.05 IU/mL.

HBV DNA

HBV DNA was assessed quantitatively using either the COBAS AmpliPrep/COBAS TaqMan HBV Test v2.0 (Roche) or the COBAS HBV assay (Roche), with a limit of quantification of 20

IU/mL and 10 IU/mL respectively. For assessing eligibility to stop NA treatment and all endpoint assessments, the lower limit of quantification was defined as <20 IU/mL.

HBeAg

HBeAg was assessed qualitatively using the Elecsys HBeAg (Roche) assay with a cut-off sensitivity of 0.24 PEIU/mL.

Anti-HBe

Anti-HBe was assessed qualitatively using the Elecsys anti-HBe assay (Roche) with a cut-off sensitivity of 0.127 IU/mL.

Anti-HBs

Anti-HBs were assessed quantitatively using the Elecsys anti-HBs II assay (Roche) with a limit of quantification of 3.5 IU/L. Anti-HBs positive was defined as anti-HBs ≥10 IU/L, and negative was defined as anti-HBs <10 IU/L.

Statistical analysis

Analyses were conducted using SAS Viya version 4 and GSK proprietary Frozen-R-4.5.1.

Sample size

The planned minimum sample size of 750 participants in each study provides >99% power to detect a statistically significant difference between treatment arms in the primary endpoint assessed by the Exact Boschloo's test with a 5% two-sided alpha level, assuming true functional cure rates of 10% for the bepirovirsen arm and 2% for the placebo arm in participants with chronic HBV infection with baseline HBsAg ≤3000 IU/mL. Assuming true functional cure rates of 15% for the bepirovirsen arm and 3% for the placebo arm among

HBsAg ≤1000 IU/mL populations, the planned minimum sample size provides 98% power to detect a statistically significant difference between treatment arms in functional cure rates assessed by the Boschloo's test with a 5% two-sided alpha level for the key secondary endpoint of functional cure in the baseline HBsAg ≤1000 IU/mL populations. Randomization could continue up to a maximum of approximately 1050 participants per study, to ensure that the number of participants across bepirovirsen clinical trials provides a sufficient safety database for submissions to regulatory authorities.

Fixed sequence hierarchical testing

Fixed sequence hierarchical testing was performed for the primary and key secondary efficacy endpoints. Each comparison was tested at a two-sided significance level of 0.05 and an overall two-sided alpha level of 0.05 was preserved. The fixed sequence was:

1. Primary outcome: Functional cure rate at Week 72 for bepirovirsen versus placebo among participants with HBsAg ≤3000 IU/mL at baseline.
2. Key secondary efficacy outcome 1: Functional cure rate at Week 72 for bepirovirsen versus placebo among participants with HBsAg ≤1000 IU/mL at baseline.
3. Key secondary efficacy outcome 2: Proportion of participants who stopped NA and had sustained HBV DNA <LLOQ (<20 IU/mL or not detected) at Week 72 for bepirovirsen versus placebo among participants with baseline HBsAg ≤3000 IU/mL.
4. Key secondary efficacy outcome 3: Proportion of participants who stopped NA and had sustained HBV DNA <LLOQ (<20 IU/mL or target not detected) at Week 72 for bepirovirsen versus placebo among participants with baseline HBsAg ≤1000 IU/mL.

Futility analysis

Prespecified interim analyses for futility, overseen by an Independent Data Monitoring Committee, were conducted by an independent statistical data analysis center after approximately 40% of participants completed the Week 24 visit and after approximately 30% of participants completed the Week 72 analysis window. The committee recommended the study continue without modification at both interim analyses.

Handling of 'blips' in HBsAg or HBV response

A HBsAg 'blip' was defined as a single HBsAg value that was positive and that was preceded by and followed by HBsAg not detected results, as assessed by HBsAg qualitative assay (limit of detection <0.05 IU/mL). A HBV DNA 'blip' was defined as a single HBV DNA value ≥LLOQ (20 IU/mL) that was preceded by and followed by HBV DNA values <LLOQ (<20 IU/mL or target not detected). Per protocol, if a potential 'blip' was recorded, a visit should occur within 1 week (±3-day window) of the first test result for confirmation.

In assessing eligibility to discontinue NA therapy and in the primary outcome analysis, HBsAg or HBV DNA 'blips' were permissible.

Primary outcome statistical analysis

The treatment effect of bepirovirsen versus placebo on the primary outcome, functional cure at Week 72 among participants with baseline HBsAg ≤3000 IU/mL, was assessed by exact Cochran-Mantel-Haenszel (CMH) test stratified by baseline HBsAg ≤1000 IU/mL and >1000 IU/mL to ≤3000 IU/mL at a 5% two-sided alpha level. Summary level of treatment effect in functional cure in participants with baseline HBsAg ≤3000 IU/mL was presented as the common risk difference and 95% Miettinen-Nurminen CI. The estimates of the common risk difference were calculated using the summary Miettinen-Nurminen (score) method and

assumed homogeneity of risk differences across strata; however, post-hoc analysis showed heterogeneity, violating the homogeneity assumption. The summary Miettinen-Nurminen (score) method used gave higher weight to the stratum with risk difference closer to 0, proportional to its inverse variance, than would be the case with a weighting based solely on subgroup size.

Key secondary outcomes statistical analyses

The treatment effect of bepirovirsen versus placebo on the key secondary outcome of functional cure at Week 72 among participants with baseline HBsAg ≤1000 IU/mL was assessed by Boschloo's test and presented as point estimate of difference in the proportion of participants with functional cure and 95% Miettinen-Nurminen CI, with a 5% two-sided alpha level. The treatment effect of bepirovirsen versus placebo on the key secondary outcome of sustained HBV DNA <LLOQ at Week 72 among participants with baseline HBsAg ≤3000 IU/mL was assessed by exact CMH test stratified by baseline HBsAg ≤1000 IU/mL and >1000 IU/mL to ≤3000 IU/mL at a 5% two-sided alpha level. Summary level of treatment effect was presented as the common risk difference and 95% Miettinen-Nurminen CI. The estimates of the common risk difference were calculated using the summary Miettinen-Nurminen (score) method and assumed homogeneity of risk differences across strata; however, post-hoc analysis showed significant heterogeneity, violating the homogeneity assumption. The summary Miettinen-Nurminen (score) method used gives higher weight to the stratum with risk difference closer to 0, proportional to its inverse variance, than would be the case with a weighting based solely on subgroup size.

The treatment effect of bepirovirsen versus placebo on the key secondary outcome of sustained HBV DNA <LLOQ at Week 72 among participants with baseline HBsAg ≤1000 IU/mL

was assessed by Boschloo's test and presented as point estimate of difference in the proportion of participants and 95% Miettinen-Nurminen CI, with a 5% two-sided alpha level.

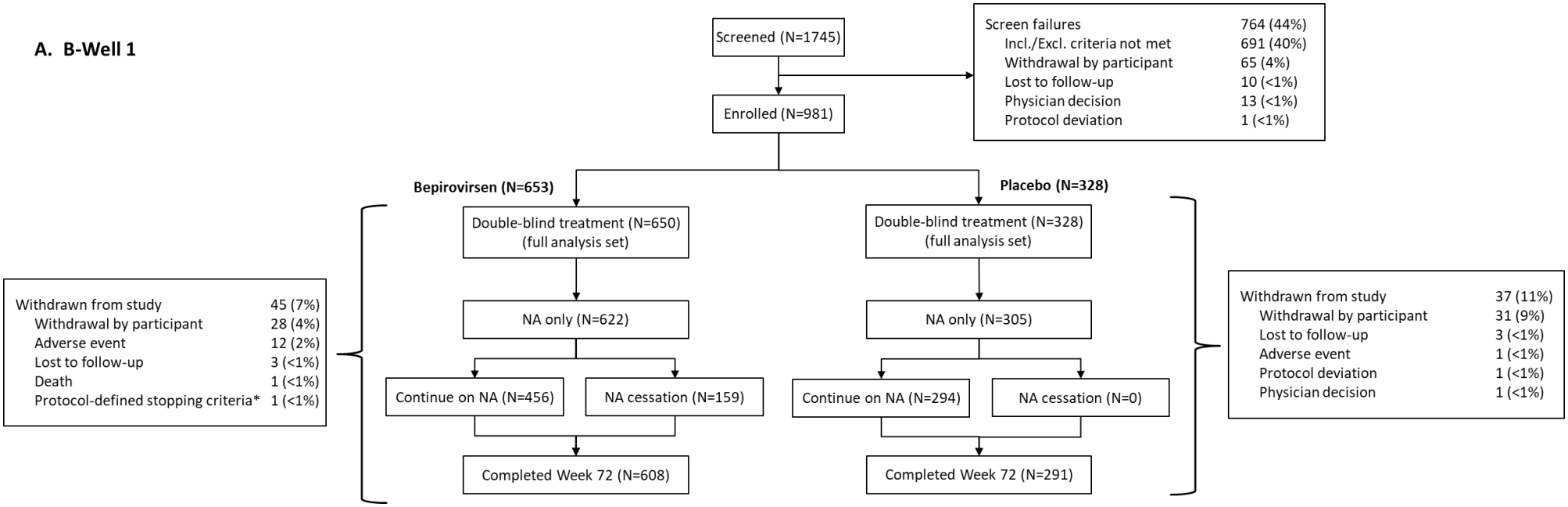
Subgroup analyses

Predefined comparison of treatment effect for subgroups was conducted with frequentist estimation, reporting the point estimate and 95% Miettinen-Nurminen CI of risk difference between treatment arms in each subgroup.

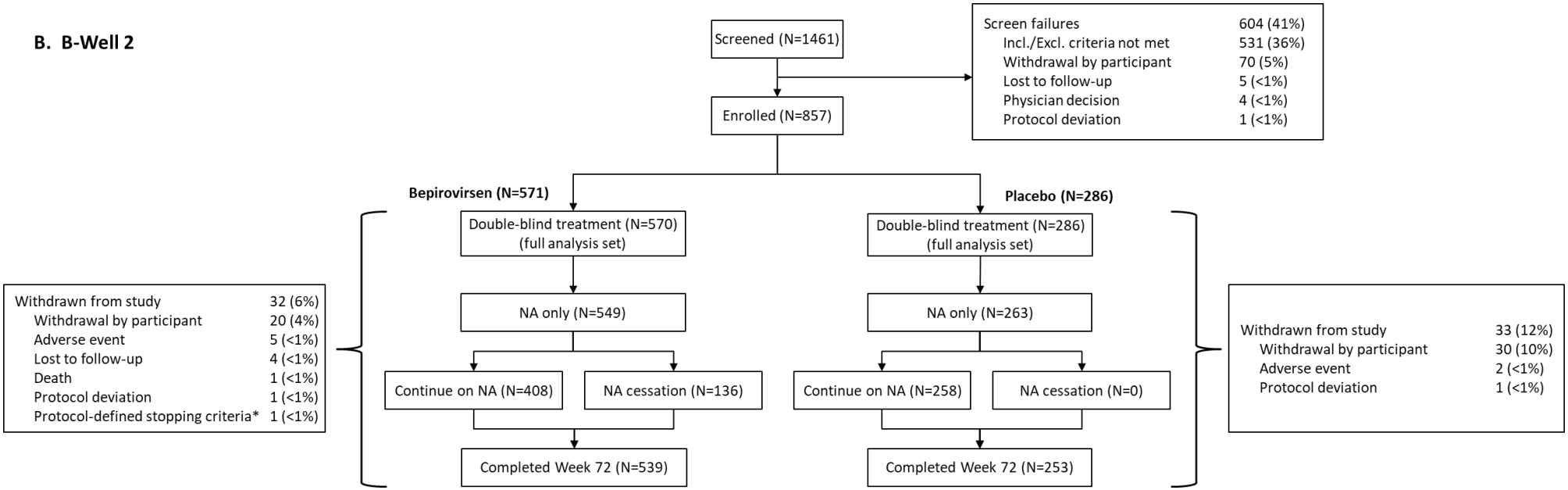
Supplementary Figures

Figure S1. Patient disposition for B-Well 1 and B-Well 2 (screened population)

A. B-Well 1



B. B-Well 2

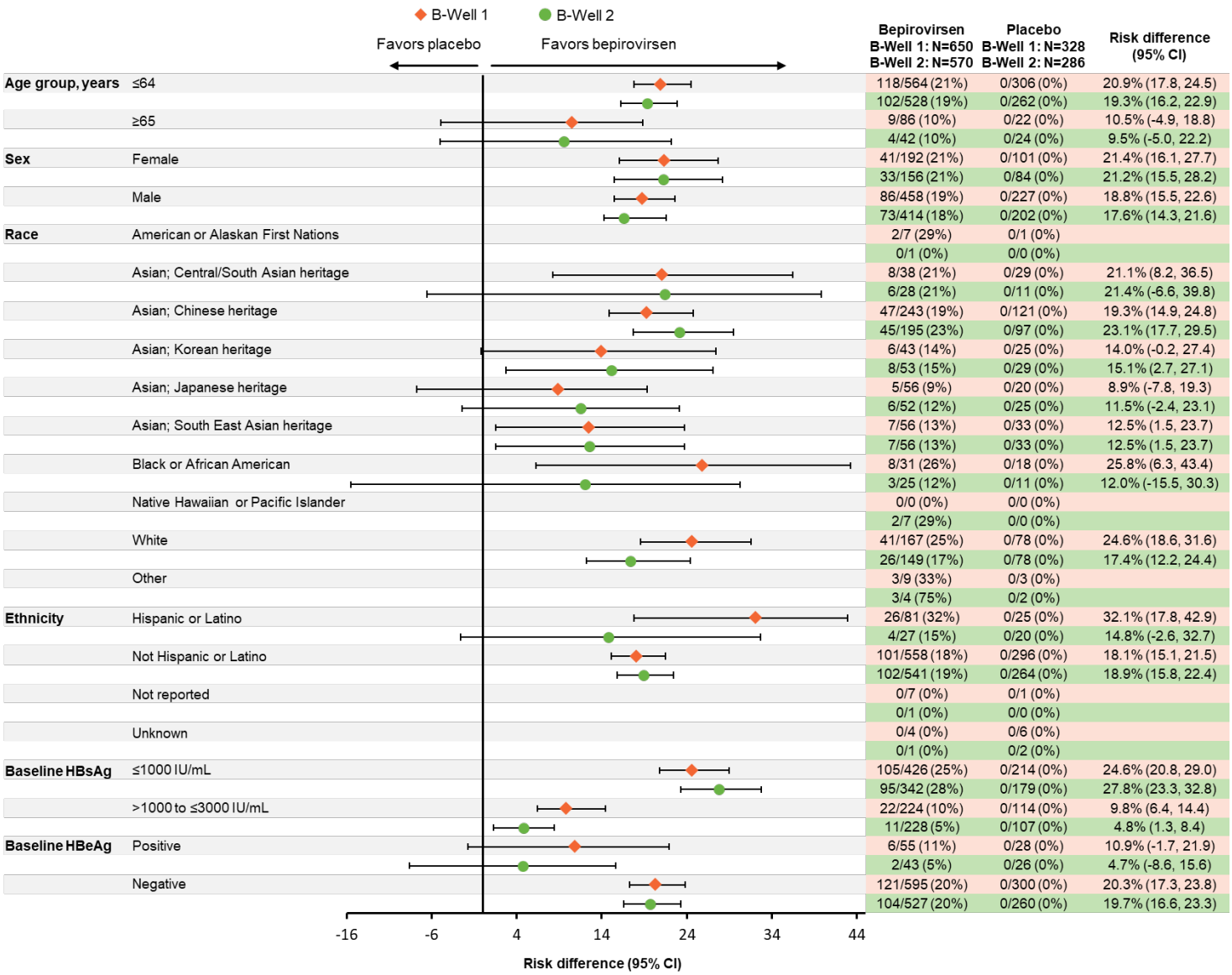


Three participants in B-Well 1 and one participant in B-Well 2 who were randomized to bepirovirsen withdrew before receiving any treatment and are not included in the respective full analysis sets. Two participants in B-Well 1 and one participant in B-well 2 who were randomized to placebo received one dose of bepirovirsen in error and are therefore included in the bepirovirsen safety population (B-Well 1, N=652; B-Well 2, N=571).

*Drug-induced vascular injury and complement stopping criteria.

Excl, exclusion; Incl, inclusion; NA, nucleos(t)ide analogue.

Figure S2. Proportion of participants with functional cure at Week 72 by subgroup

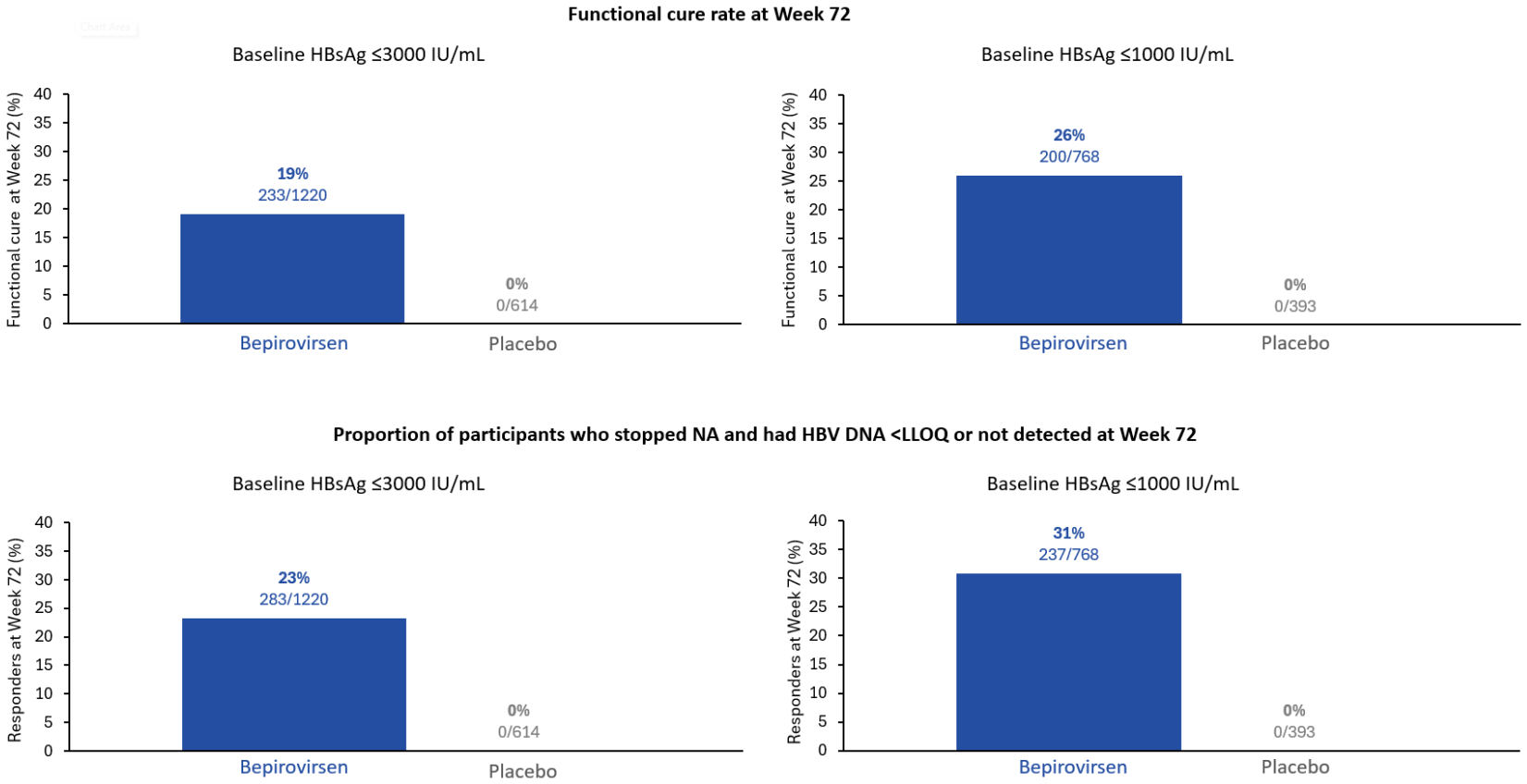


		Bepirovirsen B-Well 1: N=650 B-Well 2: N=570	Placebo B-Well 1: N=328 B-Well 2: N=286	Risk difference (95% CI)
Age group, years	≤64	118/564 (21%)	0/306 (0%)	20.9% (17.8, 24.5)
		102/528 (19%)	0/262 (0%)	19.3% (16.2, 22.9)
	≥65	9/86 (10%)	0/22 (0%)	10.5% (-4.9, 18.8)
		4/42 (10%)	0/24 (0%)	9.5% (-5.0, 22.2)
Sex	Female	41/192 (21%)	0/101 (0%)	21.4% (16.1, 27.7)
		33/156 (21%)	0/84 (0%)	21.2% (15.5, 28.2)
	Male	86/458 (19%)	0/227 (0%)	18.8% (15.5, 22.6)
		73/414 (18%)	0/202 (0%)	17.6% (14.3, 21.6)
Race	American or Alaskan First Nations	2/7 (29%)	0/1 (0%)	
		0/1 (0%)	0/0 (0%)	
	Asian; Central/South Asian heritage	8/38 (21%)	0/29 (0%)	21.1% (8.2, 36.5)
		6/28 (21%)	0/11 (0%)	21.4% (-6.6, 39.8)
	Asian; Chinese heritage	47/243 (19%)	0/121 (0%)	19.3% (14.9, 24.8)
		45/195 (23%)	0/97 (0%)	23.1% (17.7, 29.5)
	Asian; Korean heritage	6/43 (14%)	0/25 (0%)	14.0% (-0.2, 27.4)
		8/53 (15%)	0/29 (0%)	15.1% (2.7, 27.1)
	Asian; Japanese heritage	5/56 (9%)	0/20 (0%)	8.9% (-7.8, 19.3)
		6/52 (12%)	0/25 (0%)	11.5% (-2.4, 23.1)
	Asian; South East Asian heritage	7/56 (13%)	0/33 (0%)	12.5% (1.5, 23.7)
		7/56 (13%)	0/33 (0%)	12.5% (1.5, 23.7)
	Black or African American	8/31 (26%)	0/18 (0%)	25.8% (6.3, 43.4)
		3/25 (12%)	0/11 (0%)	12.0% (-15.5, 30.3)
	Native Hawaiian or Pacific Islander	0/0 (0%)	0/0 (0%)	
		2/7 (29%)	0/0 (0%)	
	White	41/167 (25%)	0/78 (0%)	24.6% (18.6, 31.6)
		26/149 (17%)	0/78 (0%)	17.4% (12.2, 24.4)
	Other	3/9 (33%)	0/3 (0%)	
		3/4 (75%)	0/2 (0%)	
Ethnicity	Hispanic or Latino	26/81 (32%)	0/25 (0%)	32.1% (17.8, 42.9)
		4/27 (15%)	0/20 (0%)	14.8% (-2.6, 32.7)
	Not Hispanic or Latino	101/558 (18%)	0/296 (0%)	18.1% (15.1, 21.5)
		102/541 (19%)	0/264 (0%)	18.9% (15.8, 22.4)
	Not reported	0/7 (0%)	0/1 (0%)	
		0/1 (0%)	0/0 (0%)	
	Unknown	0/4 (0%)	0/6 (0%)	
		0/1 (0%)	0/2 (0%)	
Baseline HBsAg	≤1000 IU/mL	105/426 (25%)	0/214 (0%)	24.6% (20.8, 29.0)
		95/342 (28%)	0/179 (0%)	27.8% (23.3, 32.8)
	>1000 to ≤3000 IU/mL	22/224 (10%)	0/114 (0%)	9.8% (6.4, 14.4)
		11/228 (5%)	0/107 (0%)	4.8% (1.3, 8.4)
Baseline HBeAg	Positive	6/55 (11%)	0/28 (0%)	10.9% (-1.7, 21.9)
		2/43 (5%)	0/26 (0%)	4.7% (-8.6, 15.6)
	Negative	121/595 (20%)	0/300 (0%)	20.3% (17.3, 23.8)
		104/527 (20%)	0/260 (0%)	19.7% (16.6, 23.3)

Comparison of treatment effect was conducted with frequentist estimation. Only subgroup levels with five or more participants within treatment arm are included in the analyses. Subgroup levels with no participants in both treatment arms are not presented.

CI, confidence interval; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen.

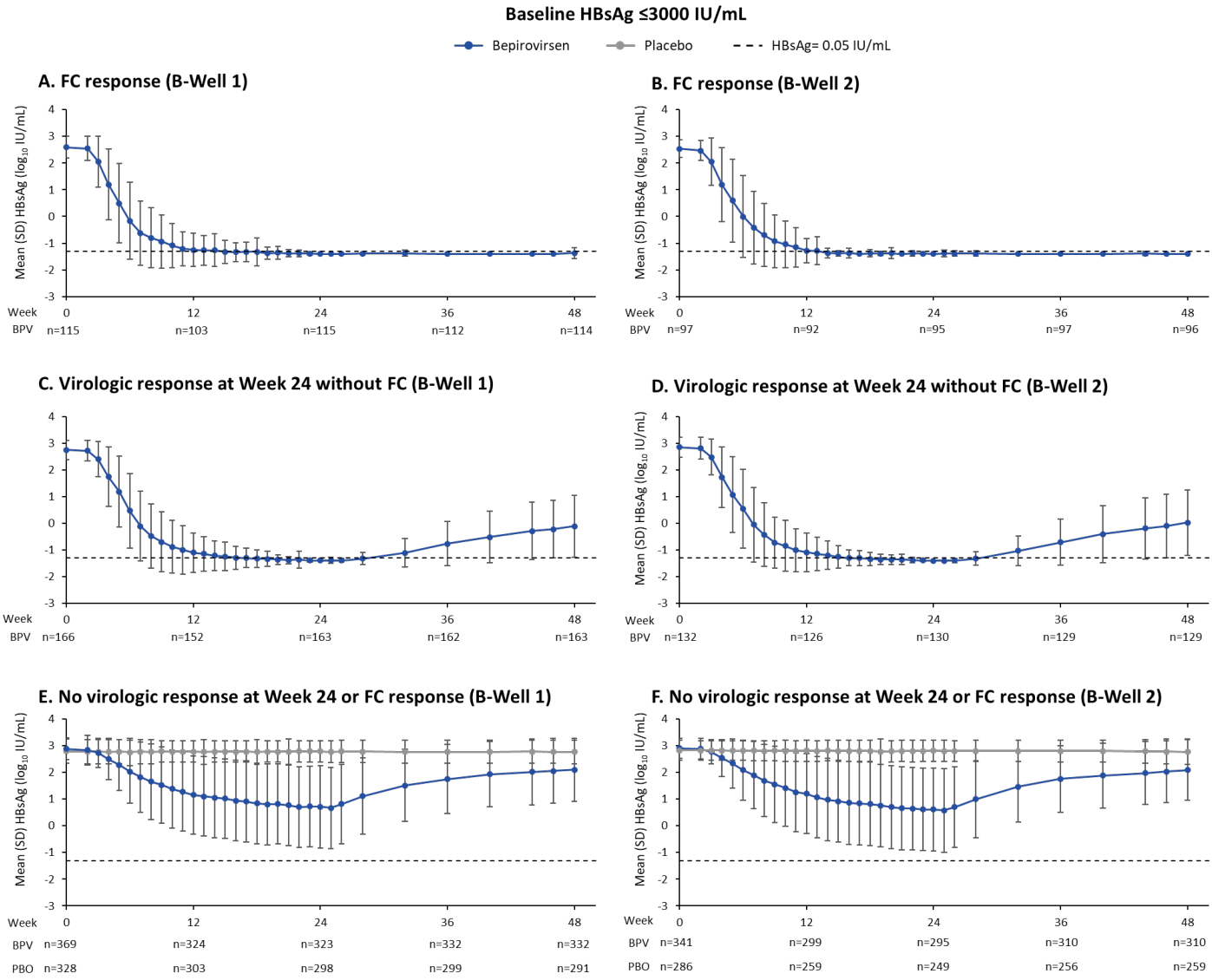
Figure S3. Efficacy analyses using pooled data from B-Well 1 and B-Well 2

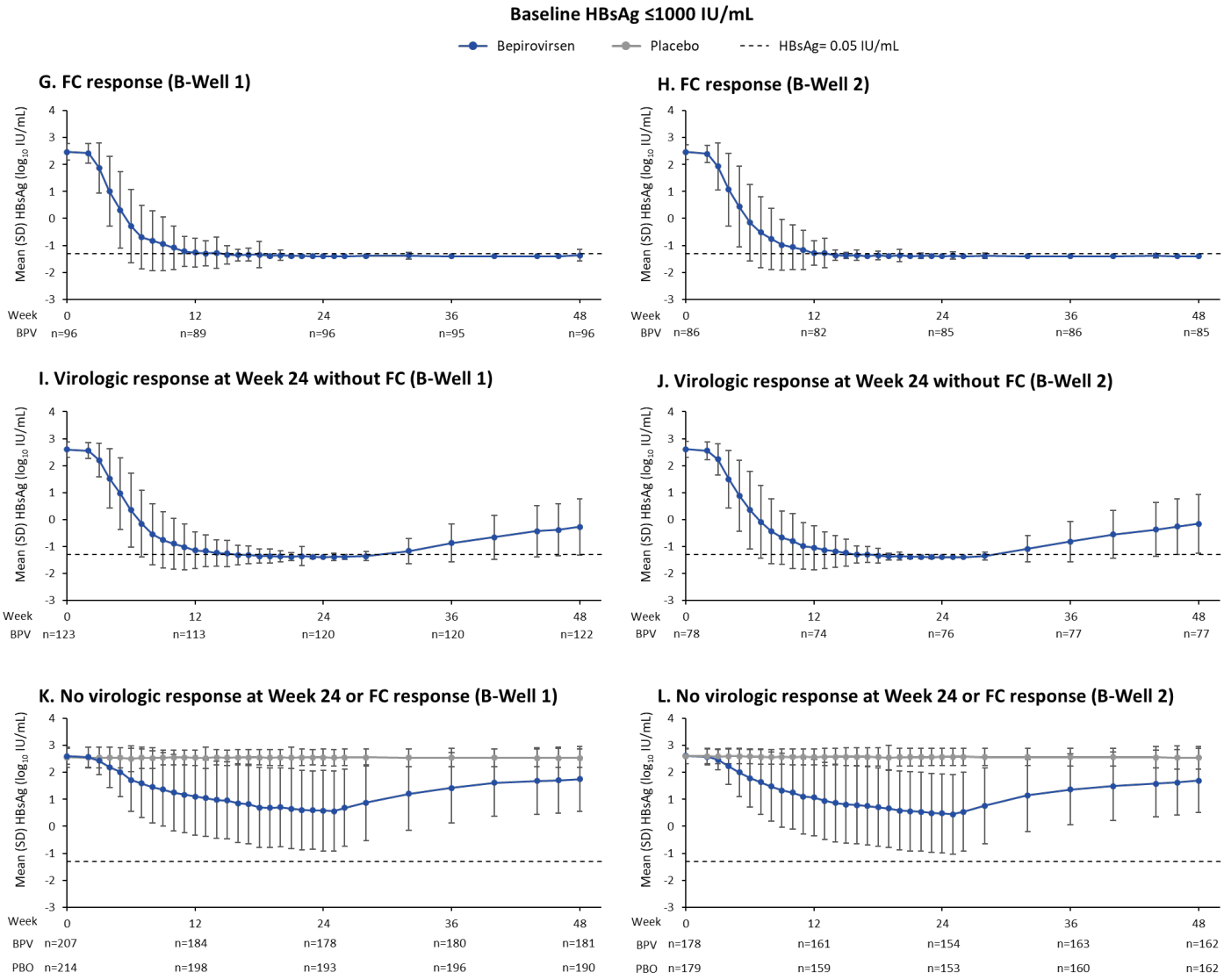


<LLOQ: <20 IU/mL or not detected.

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

Figure S4. Mean HBsAg levels to Week 48 by response status among participants with baseline HBsAg ≤3000 IU/mL and ≤1000 IU/mL

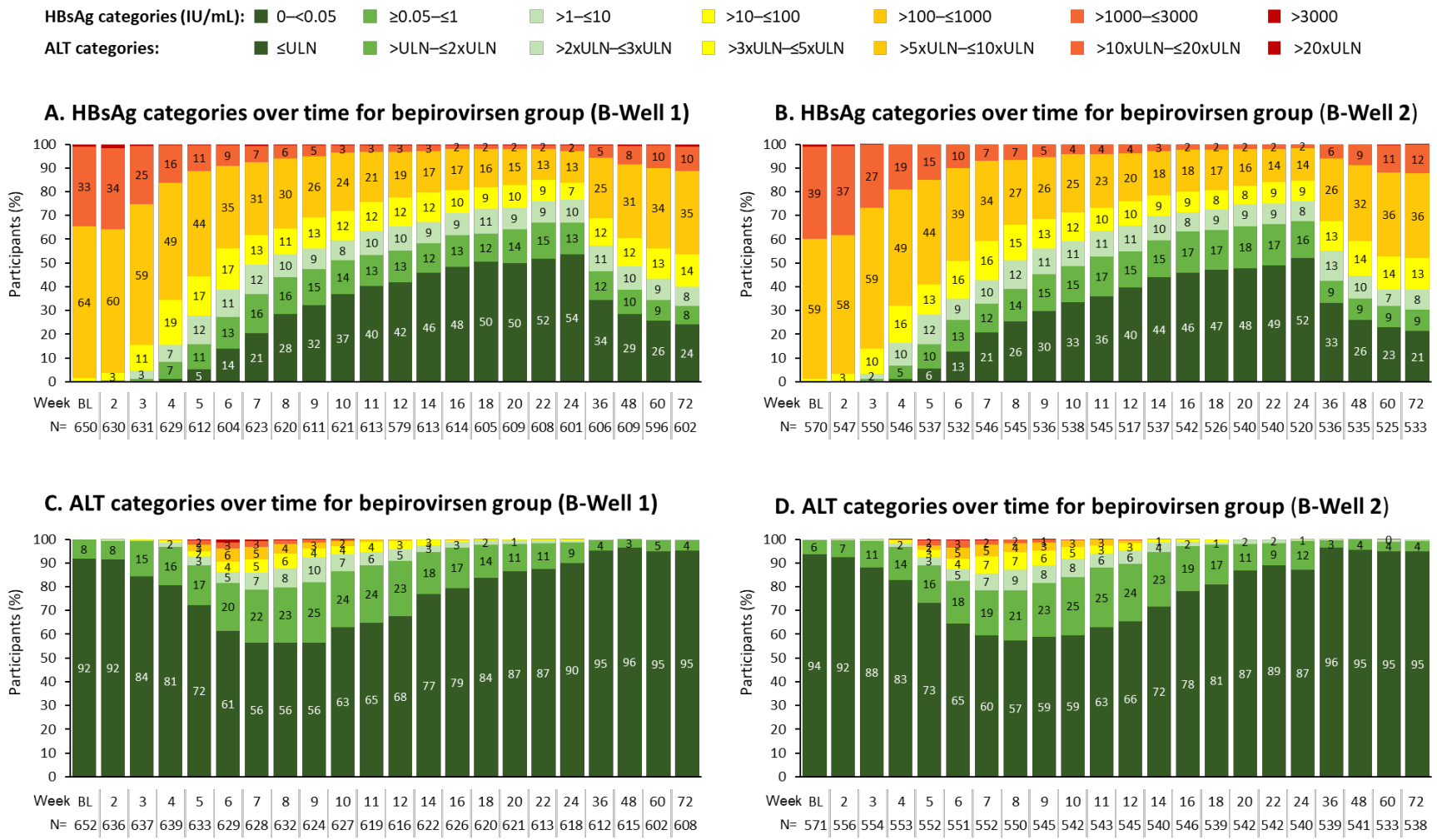




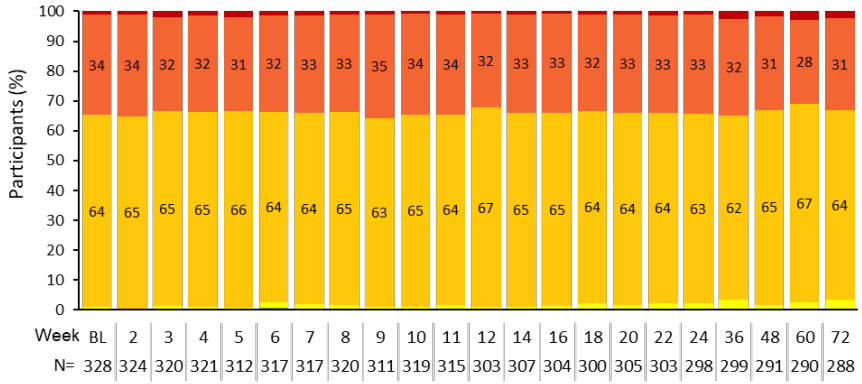
Virologic response is defined as HBsAg not detected (qualitative assay) and HBV DNA <LLOQ [<20 IU/mL] or not detected at Week 24. The “no virologic response” category may include partial responders (participants who did not discontinue NA but achieved HBsAg <1 IU/mL and HBV DNA <LLOQ at Week 72 without taking rescue medication) as well as non-responders.

FC, functional cure; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogues; SD, standard deviation.

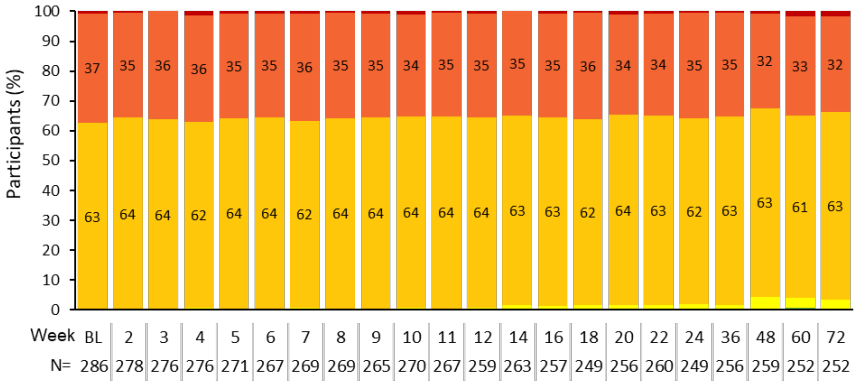
Figure S5. Proportion of participants in HBsAg and ALT categories over time



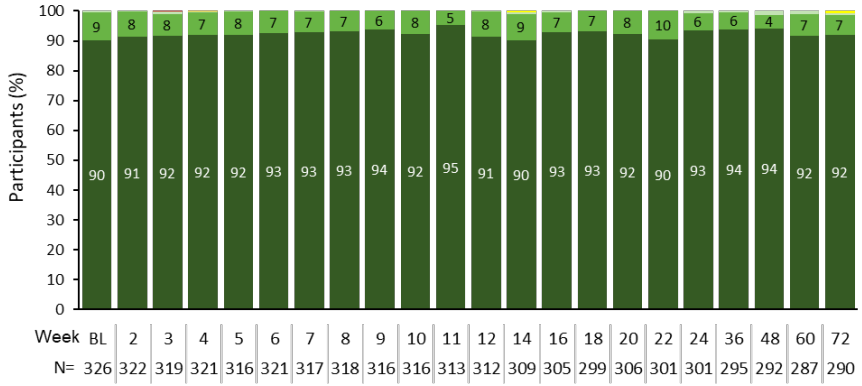
E. HBsAg categories over time for placebo group (B-Well 1)



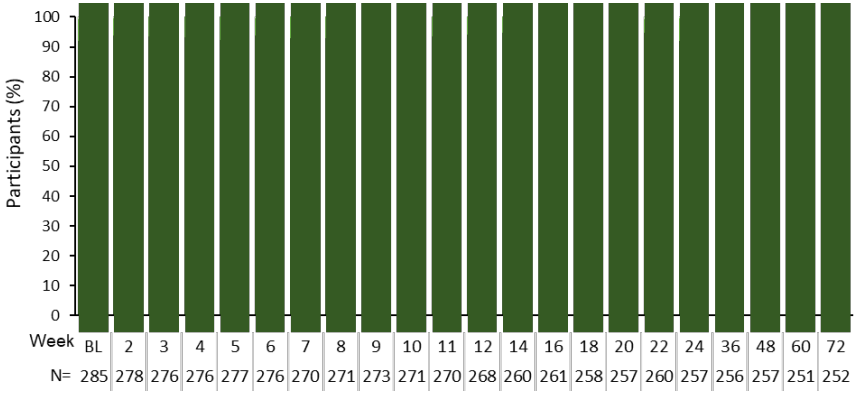
F. HBsAg categories over time for placebo group (B-Well 2)



G. ALT categories over time for placebo group (B-Well 1)



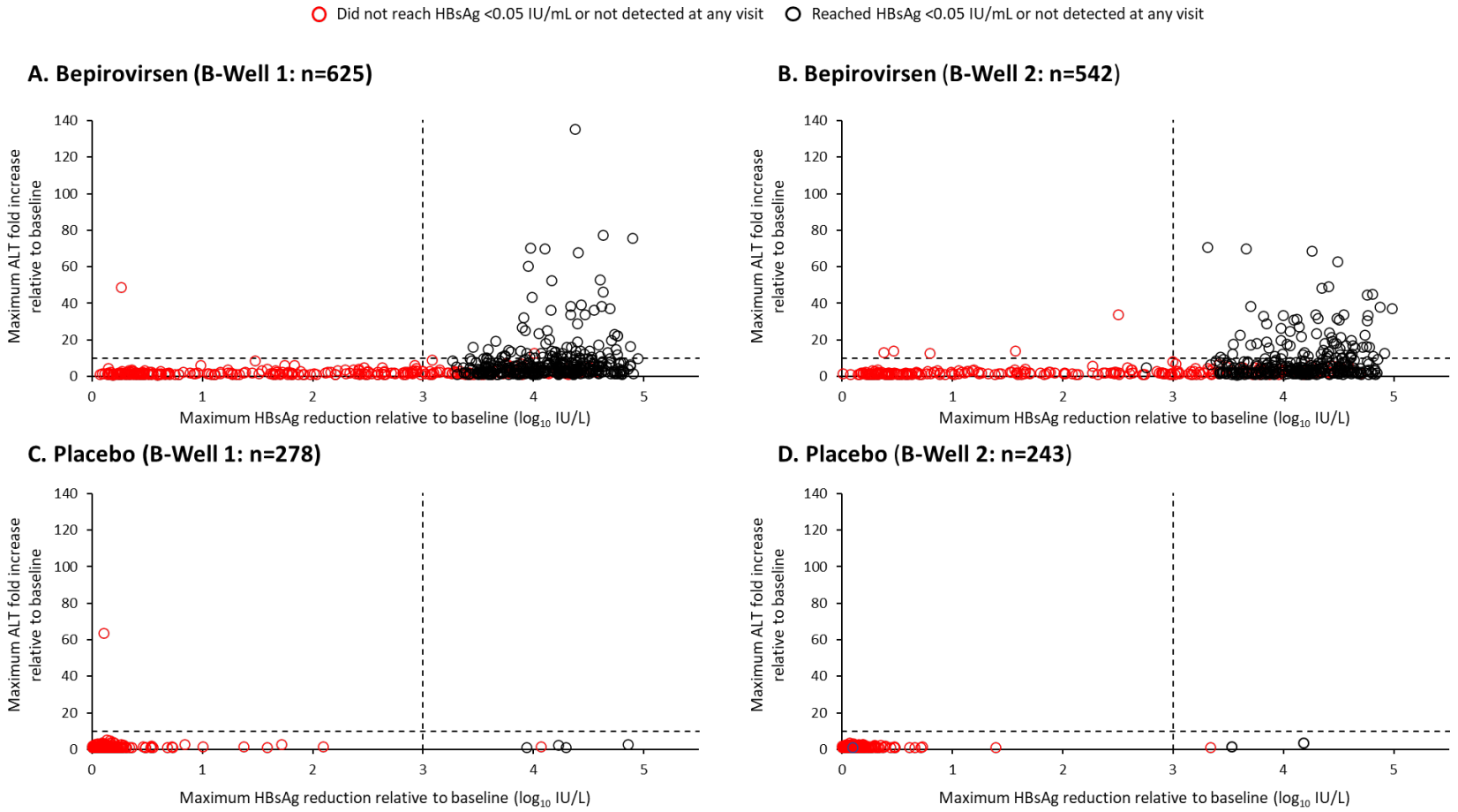
H. ALT categories over time for placebo group (B-Well 2)



Proportion of participants calculated from the number with data available for each visit.

ALT, alanine aminotransferase; BL, baseline; HBsAg, hepatitis B surface antigen; ULN, upper limit of normal.

Figure S6. Maximum ALT increase versus maximum HBsAg reduction through Week 1–24



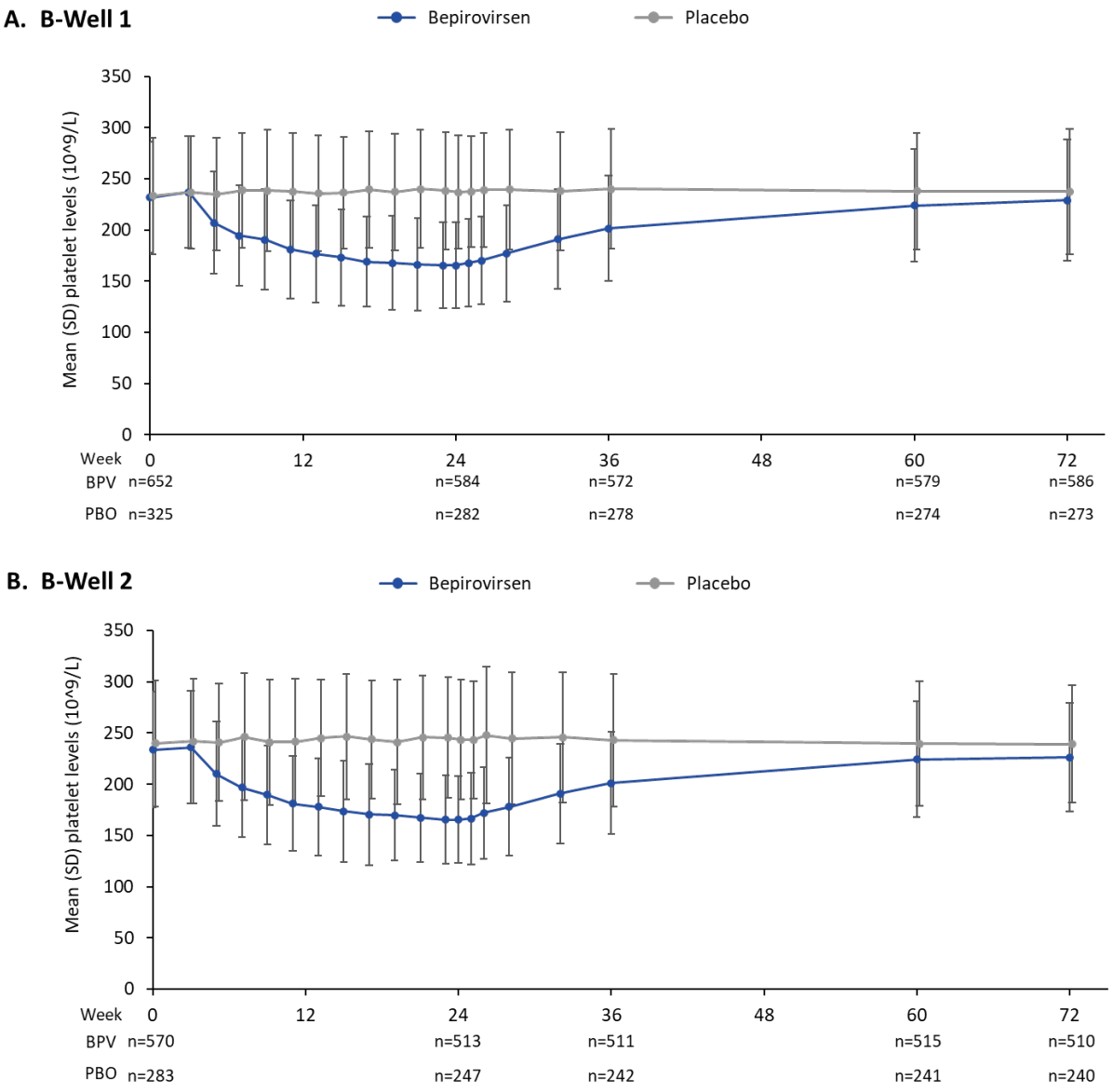
Maximum means the maximum among data points from Week 1 to 24 (inclusive), excluding values measured after rescue medication. Black or red color coding denotes reaching or not reaching HBsAg <0.05 IU/mL/not detected, respectively, at any visit for the study duration. For

placebo participants labelled as reaching HBsAg <0.05 IU/mL or not detected at any visit: one participant had natural HBsAg loss but was not eligible for NA discontinuation because they had positive HBsAg values during Weeks 24–48. The other participants in the placebo group had a single spurious negative/not detected HBsAg result.

Horizontal dashed line = maximum ALT increase 10-fold from baseline; Vertical dashed line = maximum HBsAg reduction 3 $\log_{10}$ IU/mL from baseline.

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue.

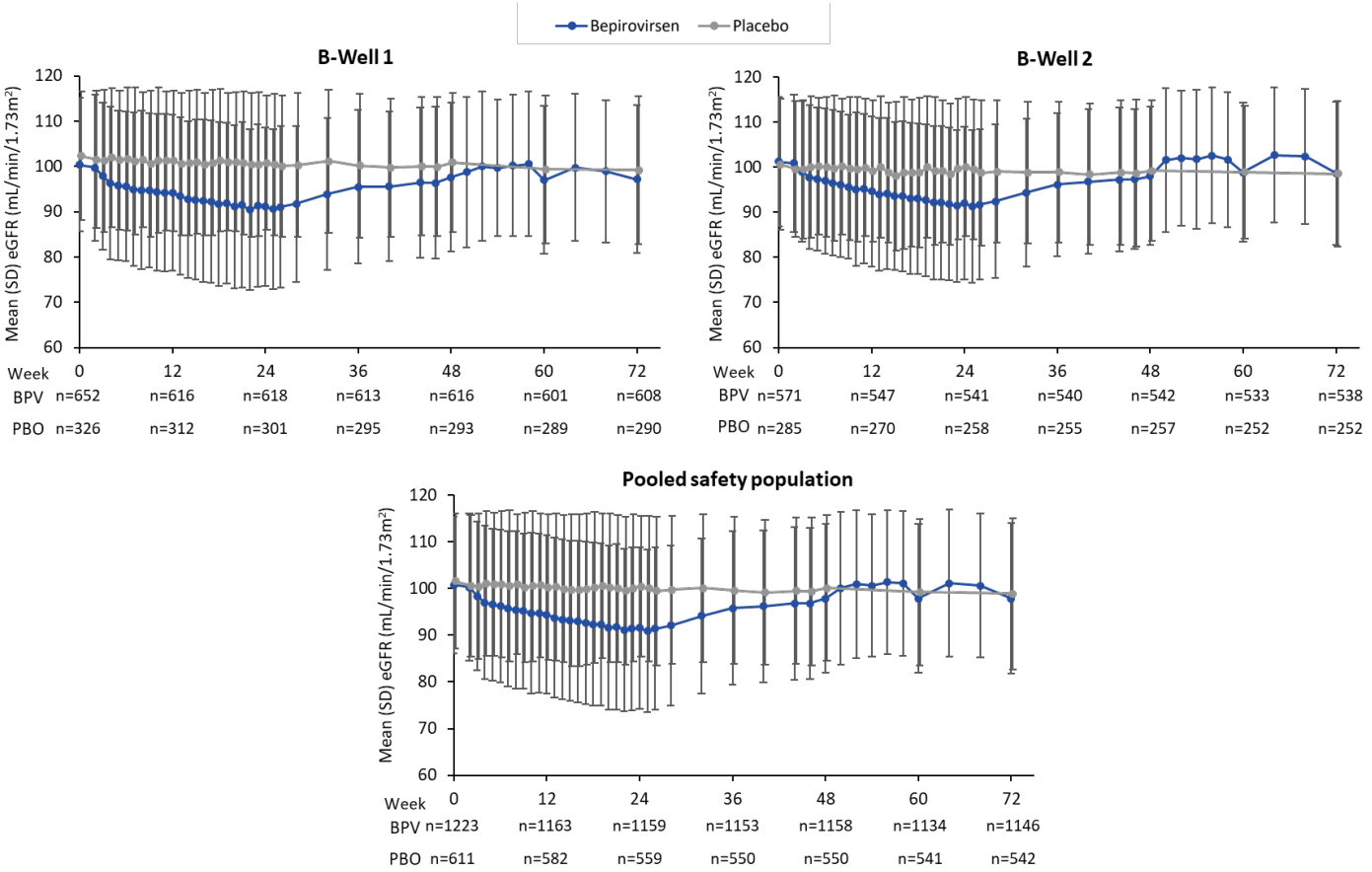
Figure S7. Mean (SD) platelet levels over 72 weeks



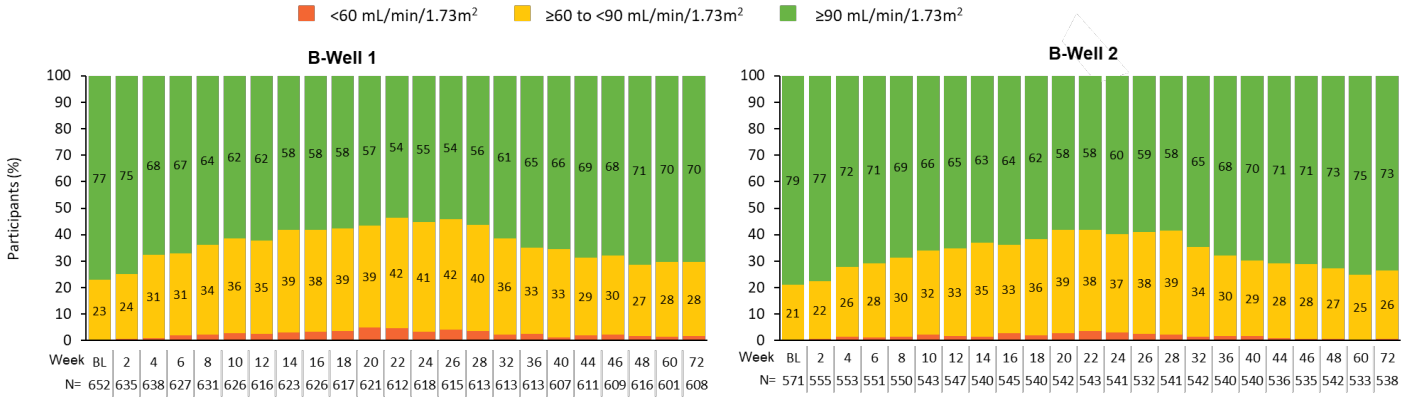
BPV, bepirovirsen; PBO, placebo; SD, standard deviation.

Figure S8. eGFR over 72 weeks expressed as A) mean (SD) (continuous values), B) categorical values (bepirovirsen treatment group) and C) categorical values (placebo treatment group)

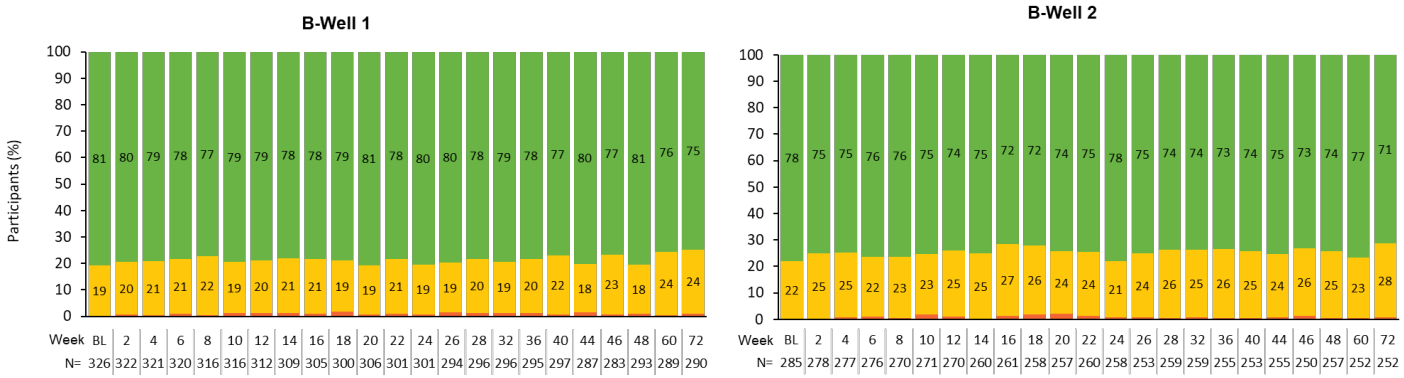
A. Mean (SD) eGFR



B. Categorical eGFR (bepirovirsen treatment group)



C. Categorical eGFR (placebo treatment group)



Proportion of participants calculated from the number with data available for each visit.

BL, baseline; BPV, bepirovirsen; PBO, placebo; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Supplementary Tables

Table S1. Representativeness of study participants

Category	Example
Disease, problem, or condition under investigation	Chronic HBV infection
Special considerations related to:	
Sex	Chronic HBV infection is more common in men than women, with an overall male-to-female ratio of approximately 1.4:1 across geographies.[1-3] Among people with chronic HBV and HBsAg level ≤3000 IU/mL, the male-to-female ratio may be lower, reported as 1.2:1 in the UK.[4]
Age	In the USA, the highest rates of newly reported chronic hepatitis B occur in people aged 30–39 and 40–49; together, they account for approximately 46% of all new chronic hepatitis B cases.[3] A multicountry study (US, Germany, and Taiwan) reports similar prevalence trends in each country, with the highest prevalence in the 50–

	<65 age group.[5] Among people with chronic HBV infection and HBsAg level ≤3000 IU/mL, the mean age is 50 years old in the UK.[4]
Race or ethnic group	Race, ethnicity, or geographical lineage is important to consider in patients with chronic HBV infection because HBV genotypes commonly vary by region.[6,7] In the United Sates, the Asian population is disproportionately highly represented in HBV infection cases.[3,8] The rate of newly reported chronic hepatitis B cases among non-Hispanic Asian/Pacific Islander persons (18.9 cases per 100,000 population) was >9.9 times greater than among non-Hispanic White persons (1.9 cases per 100,000 population).[3] In a UK study, approximately 41% of people with chronic HBV infection and HBsAg level ≤3000 IU/mL are reported as Asian.[4]
Geography	China is the country with the most cases of HBV infection.[9] China, India, and Indonesia represent 50% of the global HBV burden, and nine countries in Asia and Africa account for approximately 70% of the global burden.[10] Country-specific prevalence of chronic HBV infection is highest in WHO African and Western Pacific regions, where chronic HBV infection affects 5.8% and 5.0% of the general population, respectively. [10]
Other considerations	Chronic HBV infection has heterogeneous clinical expression.[4]

	All patients with HBsAg and detectable HBV DNA are candidates for antiviral therapy, with personalized treatment decisions considering HBeAg status, HBV DNA levels, ALT levels, fibrosis stage, HDV or HIV co-infection, and risk of liver disease progression of hepatocellular carcinoma.[4]
Overall representativeness of this trial	This study selected patients with chronic HBV infection with HBsAg ≤3000 IU/mL because previous data indicated greater efficacy with bepirovirsen for patients at or below this threshold.[11] There are limited real-world data defining demographic characteristics for patients with HBsAg ≤3000 IU/mL specifically. Nonetheless, the demographics of the patients in the B-Well trials are broadly representative of global data for adults with chronic HBV infection, and consistent with limited real-world evidence from a UK cohort with HBsAg ≤3000 IU/mL.[4] In the B-Well trials, the majority of participants were males, with a male-to-female ratio of 2.35:1 in B-Well 1 and 2.56 in B-Well 2, the majority of participants were Asian (68%; both studies), and the mean age ranged from 49 to 50 years across treatment arms and studies. People with HCV, HDV, or HIV co-infection were excluded from this study. However, the prevalence of these populations is low, and efficacy and safety in this population will be assessed in a separate study (NCT06497504).[6]

EASL, European Association for the Study of the Liver; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; 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. The information and interpretation were reviewed by the authors.

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Table S2. Participants who discontinued NAs: Overall and without FC

	B-Well 1				B-Well 2			
	Baseline HBsAg ≤3000 IU/mL		Baseline HBsAg ≤1000 IU/mL		Baseline HBsAg ≤3000 IU/mL		Baseline HBsAg ≤1000 IU/mL	
	Bepirovirsen N=650	Placebo N=328	Bepirovirsen N=426	Placebo N=214	Bepirovirsen N=570	Placebo N=286	Bepirovirsen N=342	Placebo N=179
Discontinued NAs at Week 48, n (%)	159 (24)	0 (0)	131 (31)	0 (0)	136 (24)	0 (0)	114 (33)	0 (0)
Discontinued NAs, but did not achieve FC, n (%)	32 (5)	0 (0)	26 (6)	0 (0)	30 (5)	0 (0)	19 (6)	0 (0)
Reasons for FC failure, n (%)*								
Virologic relapse (without clinical relapse)†	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Clinical relapse†	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rescue medication	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Confirmed HBV DNA elevation at Week 72	3 (9)	0 (0)	2 (8)	0 (0)	2 (7)	0 (0)	0 (0)	0 (0)
Confirmed HBsAg elevation at Week 72	27 (84)	0 (0)	22 (85)	0 (0)	29 (97)	0 (0)	19 (100)	0 (0)
Other[‡]	6 (19)	0 (0)	5 (19)	0 (0)	2 (7)	0 (0)	1 (5)	0 (0)

*Participants may have more than one reason for failure; percentages of reasons for FC failure are based on the number of participants who achieved NA cessation but did not achieve FC. [†]Virologic relapse was defined as HBV DNA >2000 IU/mL at two sequential visits after cessation of NA treatment having previously achieved virologic response, with the initial value confirmed within 1 week (±3 days); clinical relapse was defined as HBV DNA >2000 IU/mL and ALT >2xULN at two sequential visits after cessation of NA treatment having previously achieved virologic response, with the HBV DNA value confirmed within 1 week (±3 days) from the date of the first result. [‡]"Other" includes (1) missing data in Week 72 visit analysis window and lack of two surrounding measurements of HBV DNA <LLOQ or not detected or HBsAg not detected, without previous occurrence of virologic relapse, clinical relapse, or rescue medication, (2) HBV DNA ≥LLOQ or HBsAg positive in Week 72 analysis window following previous HBV DNA <LLOQ or not detected or HBsAg not detected and the subsequent measurement is missing, and (3) restarting NA not for the purpose of HBV control (HBV relapse).

ALT, alanine aminotransferase; FC, functional cure; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; ULN, upper limit of normal.

Table S3. Functional cure rate at Week 72 in HBsAg ≤1000 IU/mL and >1000 IU/mL strata

	B-Well 1			B-Well 2		
	Functional cure response, n/N (%)		% Risk difference (95% CI)*,†	Functional cure response, n/N (%)		% Risk difference (95% CI)*,†
	Bepirovirsen N=650	Placebo N=328		Bepirovirsen N=570	Placebo N=286	
Baseline HBsAg ≤3000 IU/mL	127/650 (20)	0/328	17.5 (14.6, 20.3)*	106/570 (19)	0/286	13.3 (10.4, 16.1)*
Baseline HBsAg ≤1000 IU/mL	105/426 (25)	0/214	24.6 (20.8, 29.0)†	95/342 (28)	0/179	27.8 (23.3, 32.8)†
Baseline HBsAg >1000 to ≤3000 IU/mL	22/224 (10)	0/114	9.8 (6.4, 14.4)†	11/228 (5)	0/107	4.8 (1.3, 8.4)†

*For participants with baseline HBsAg ≤3000 IU/mL, the estimate of the common risk difference assumes homogeneity of risk differences between the baseline HBsAg ≤1000 IU/mL and >1000 IU/mL strata, and was calculated using the summary Miettinen-Nurminen (score) method. This method gives higher weight to the stratum with risk difference closer to 0, proportional to its inverse variance, than would be the

case with a weighting based solely on subgroup size. [†]For participants in the baseline HBsAg ≤1000 IU/mL strata, the treatment effect was summarized by the risk difference and 95% Miettinen-Nurminen CI.

CI, confidence interval; FC, functional cure; HBsAg, hepatitis B surface antigen.

Table S4. Proportion of participants with sustained HBV DNA <LLOQ at Week 72 after NA discontinuation, by FC status

	B-Well 1		B-Well 2	
	Bepirovirsen N=650	**Placebo N=328**	**Bepirovirsen N=570**	**Placebo N=286**
Baseline HBsAg ≤3000 IU/mL + discontinued NA	**159**	**0**	**136**	**0**
HBV DNA <LLOQ and FC at Week 72, n (%)*	127 (80)	0	106 (78)	0
HBV DNA <LLOQ without FC at Week 72, n (%)*	24 (15)	0	26 (19)	0
No sustained HBV DNA <LLOQ at Week 72, n (%)*	8 (5)	0	4 (3)	0
Baseline HBsAg <1000 IU/mL + discontinued NA	**131**	**0**	**114**	**0**
HBV DNA <LLOQ and FC at Week 72, n (%)*	105 (80)	0	95 (83)	0
HBV DNA <LLOQ without FC at Week 72, n (%)*	19 (15)	0	18 (16)	0
No sustained HBV DNA <LLOQ at Week 72, n (%)*	7 (5)	0	1 (<1)	0

HBV DNA <LLOQ was defined as <20 IU/mL or target not detected. Functional cure was defined as HBV DNA <LLOQ or target not detected and HBsAg not detected.

*Percentage calculated from number of participants who discontinued NA in relevant HBsAg strata.

FC, functional cure; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue.

Table S5. Summary of selected hematological, hepatobiliary, and renal abnormalities

A. B-Well 1

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**
Hematological laboratory abnormalities								
Participants with at least 1 post baseline platelet measurement, n (%)	643 (99)	324 (>99)	623 (96)	301 (92)	154 (24)	0	451 (69)	287 (88)
Platelets <100x10^9/L, n (%)								
At any visit	51 (8)	1 (<1)	23 (4)	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
At ≥2 consecutive visits	16 (2)	1 (<1)	4 (<1)	1 (<1)	0	0	1 (<1)	0
At >1 non-consecutive visits	17 (3)	0	1 (<1)	0	0	0	0	0
Platelets <75x10^9/L, n (%)								

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
At any visit	8 (1)	1 (<1)	1 (<1)	1 (<1)	0	0	0	0
At ≥2 consecutive visits	2 (<1)	0	0	1 (<1)	0	0	0	0
At >1 non-consecutive visits	1 (<1)	1 (<1)	0	0	0	0	0	0
Platelets <50x10^9/L, n (%)								
At any visit	2 (<1)	0	0	0	0	0	0	0
At ≥2 consecutive visits	0	0	0	0	0	0	0	0
At >1 non-consecutive visits	0	0	0	0	0	0	0	0
Renal laboratory abnormalities								

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
Participants with at least 1 post baseline serum creatinine measurement, n (%)	646 (>99)	325 (>99)	623 (96)	302 (93)	158 (24)	0	454 (70)	290 (89)
Serum creatinine >0.3 mg/dL change from baseline, n (%)								
At any visit	121 (19)	23 (7)	57 (9)	13 (4)	7 (1)	0	9 (1)	4 (1)
At ≥2 consecutive visits	29 (4)	6 (2)	15 (2)	1 (<1)	1 (<1)	0	2 (<1)	0
At >1 non-consecutive visits	39 (6)	6 (2)	9 (1)	0	2 (<1)	0	0	0
Serum creatinine >0.5 mg/dL change from baseline, n (%)								
At any visit	16 (2)	5 (2)	8 (1)	3 (<1)	1 (<1)	0	1 (<1)	1 (<1)
At ≥2 consecutive visits	2 (<1)	2 (<1)	2 (<1)	0	1 (<1)	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
At >1 non-consecutive visits	2 (<1)	0	1 (<1)	1 (<1)	0	0	0	0
Participants with at least 1 post baseline eGFR measurement, n (%)	646 (>99)	325 (>99)	623 (96)	302 (93)	158 (24)	0	454 (70)	290 (89)
eGFR >30% reduction from baseline, n (%)								
At any visit	110 (17)	21 (6)	51 (8)	7 (2)	4 (<1)	0	6 (<1)	4 (1)
At ≥2 consecutive visits	30 (5)	5 (2)	13 (2)	2 (<1)	1 (<1)	0	0	0
At >1 non-consecutive visits	46 (7)	3 (<1)	12 (2)	0	1 (<1)	0	0	0
eGFR >50% reduction from baseline, n (%)								
At any visit	8 (1)	3 (<1)	2 (<1)	2 (<1)	0	0	1 (<1)	1 (<1)
At ≥2 consecutive visits	1 (<1)	2 (<1)	0	0	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
At >1 non-consecutive visits	1 (<1)	0	0	0	0	0	0	0
Participants with at least 1 post baseline urine ACR: measurement, n (%)	643 (99)	324 (>99)	623 (96)	302 (93)	NA**	NA**	NA**	NA**
Urine ACR >300 mg/g, n (%)								
At any visit	12 (2)	6 (2)	8 (1)	4 (1)	NA	NA	NA	NA
At ≥2 consecutive visits	3 (<1)	1 (<1)	2 (<1)	1 (<1)	NA	NA	NA	NA
At >1 non-consecutive visits	3 (<1)	1 (<1)	1 (<1)	0	NA	NA	NA	NA
Urine ACR >500 mg/g, n (%)								
At any visit	9 (1)	5 (2)	4 (<1)	2 (<1)	NA	NA	NA	NA

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
At ≥2 consecutive visits	2 (<1)	0	2 (<1)	0	NA	NA	NA	NA
At >1 non-consecutive visits	2 (<1)	0	0	0	NA	NA	NA	NA
Urine ACR >1000 mg/g, n (%)								
At any visit	5 (<1)	2 (<1)	1 (<1)	1 (<1)	NA	NA	NA	NA
At ≥2 consecutive visits	1 (<1)	0	0	0	NA	NA	NA	NA
At >1 non-consecutive visits	1 (<1)	0	0	0	NA	NA	NA	NA
Urine ACR >2000 mg/g, n (%)								
At any visit	2 (<1)	0	0	0	NA	NA	NA	NA
At ≥2 consecutive visits	0	0	0	0	NA	NA	NA	NA
At >1 non-consecutive visits	1 (<1)	0	0	0	NA	NA	NA	NA

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
Urine sediment, n (%)								
Participants with at least 1 urine sediment measurement, n (%)	470 (72)	234 (72)	408 (63)	180 (55)	NA**	NA**	NA**	NA**
At any visit	141 (22)	60 (18)	84 (13)	44 (13)	NA	NA	NA	NA
≥5 RBC/HPF	93 (14)	37 (11)	48 (7)	24 (7)	NA	NA	NA	NA
≥5 WBC/HPF	81 (12)	37 (11)	52 (8)	29 (9)	NA	NA	NA	NA
RBC casts	0	0	0	0	NA	NA	NA	NA
WBC casts	0	0	0	0	NA	NA	NA	NA
Hepatobiliary laboratory abnormalities								

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
Participants with at least 1 post baseline ALT and BIL measurement, n (%)	646 (>99)	325 (>99)	623 (96)	302 (93)	158 (24)	0	454 (70)	290 (89)
ALT ≥3xULN and BIL ≥2xULN*, n (%)	0	0	1 (<1)[§]	0	0	0	0	0
Participants with at least 1 post baseline ALT, BIL and ALP measurement, n (%)	646 (>99)	325 (>99)	623 (96)	302 (93)	158 (24)	0	454 (70)	290 (89)
ALT ≥3xULN and BIL ≥2xULN and ALP <2xULN, n (%)	0	0	1 (<1)	0	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
ALT and INR: Participants with at least 1 post baseline ALT and INR measurement, n (%)	254 (39)	105 (32)	22 (3)	12 (4)	1 (<1)	0	0	0
ALT ≥3xULN and INR >1.5†, n (%)	0	0	0	0	0	0	0	0
Hepatocellular injury: Participants with at least 1 post baseline ALT and ALP measurement on the same day, n (%)	646 (>99)	325 (>99)	623 (96)	302 (93)	158 (24)	0	454 (70)	290 (89)
Hepatocellular injury‡, n (%)	119 (18)	2 (<1)	3 (<1)	0	0	0	0	2 (<1)
Hepatocellular injury and BIL: Participants with at least 1 post baseline ALT and ALP measurement on	646 (>99)	325 (>99)	623 (96)	302 (93)	158 (24)	0	454 (70)	290 (89)

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
the same day and at least 1 BIL measurement, n (%)								
Hepatocellular injury‡ and BIL ≥2xULN, n (%)	0	0	0	0	0	0	0	0
Participants with at least 1 post baseline ALT, n (%)	646 (>99)	325 (>99)	623 (96)	302 (93)	158 (24)	0	454 (70)	290 (89)
ALT ≥3xULN, n (%)	150 (23)	2 (<1)	6 (<1)	1 (<1)	0	0	0	2 (<1)
ALT ≥5xULN, n (%)	88 (14)	1 (<1)	2 (<1)	0	0	0	0	0
ALT ≥8xULN, n (%)	51 (8)	1 (<1)	0	0	0	0	0	0
ALT ≥10xULN, n (%)	37 (6)	1 (<1)	0	0	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326
ALT ≥20xULN, n (%)	14 (2)	1 (<1)	0	0	0	0	0	0

B. B-Well 2

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
Hematological laboratory abnormalities								
Participants with at least 1 post baseline platelet measurement, n (%)	560 (98)	280 (98)	545 (95)	262 (92)	135 (24)	0	405 (71)	252 (88)

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
Platelets <100x10^9/L, n (%)								
At any visit	49 (9)	2 (<1)	30 (5)	0	0	0	2 (<1)	0
At ≥2 consecutive visits	17 (3)	0	6 (1)	0	0	0	0	0
At >1 non-consecutive visits	19 (3)	0	2 (<1)	0	0	0	0	0
Platelets <75x10^9/L, n (%)								
At any visit	9 (2)	0	5 (<1)	0	0	0	0	0
At ≥2 consecutive visits	3 (<1)	0	0	0	0	0	0	0
At >1 non-consecutive visits	2 (<1)	0	0	0	0	0	0	0
Platelets <50x10^9/L, n (%)								
At any visit	0	0	0	0	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
At ≥2 consecutive visits	0	0	0	0	0	0	0	0
At >1 non-consecutive visits	0	0	0	0	0	0	0	0
Renal laboratory abnormalities								
Participants with at least 1 post baseline serum creatinine measurement, n (%)	564 (99)	281 (99)	547 (96)	262 (92)	136 (24)	0	407 (71)	256 (90)
Serum creatinine >0.3 mg/dL change from baseline, n (%)								
At any visit	98 (17)	22 (8)	54 (9)	8 (3)	3 (<1)	0	1 (<1)	2 (<1)
At ≥2 consecutive visits	24 (4)	5 (2)	6 (1)	0	0	0	0	0
At >1 non-consecutive visits	34 (6)	5 (2)	11 (2)	1 (<1)	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
Serum creatinine >0.5 mg/dL change from baseline, n (%)								
At any visit	15 (3)	4 (1)	3 (<1)	1 (<1)	0	0	0	0
At ≥2 consecutive visits	2 (<1)	0	0	0	0	0	0	0
At >1 non-consecutive visits	3 (<1)	0	0	0	0	0	0	0
Participants with at least 1 post baseline eGFR measurement, n (%)	564 (99)	281 (99)	547 (96)	262 (92)	136 (24)	0	407 (71)	256 (90)
eGFR >30% reduction from baseline, n (%)								
At any visit	84 (15)	18 (6)	43 (8)	4 (1)	3 (<1)	0	2 (<1)	2 (<1)
At ≥2 consecutive visits	21 (4)	2 (<1)	8 (1)	0	0	0	0	0
At >1 non-consecutive visits	32 (6)	2 (<1)	14 (2)	0	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
eGFR >50% reduction from baseline, n (%)								
At any visit	6 (1)	2 (<1)	1 (<1)	0	0	0	0	0
At ≥2 consecutive visits	0	0	0	0	0	0	0	0
At >1 non-consecutive visits	0	0	0	0	0	0	0	0
Participants with at least 1 post baseline urine ACR measurement, n (%)	561 (98)	280 (98)	547 (96)	261 (92)	NA**	NA**	NA**	NA**
Urine ACR >300 mg/g, n (%)								
At any visit	6 (1)	1 (<1)	5 (<1)	2 (<1)	NA	NA	NA	NA
At ≥2 consecutive visits	1 (<1)	0	1 (<1)	0	NA	NA	NA	NA
At >1 non-consecutive visits	0	1 (<1)	0	1 (<1)	NA	NA	NA	NA

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
Urine ACR >500 mg/g, n (%)								
At any visit	4 (<1)	0	1 (<1)	0	NA	NA	NA	NA
At ≥2 consecutive visits	1 (<1)	0	1 (<1)	0	NA	NA	NA	NA
At >1 non-consecutive visits	0	0	1 (<1)	0	NA	NA	NA	NA
Urine ACR >1000 mg/g, n (%)								
At any visit	1 (<1)	0	1 (<1)	0	NA	NA	NA	NA
At ≥2 consecutive visits	0	0	0	0	NA	NA	NA	NA
At >1 non-consecutive visits	0	0	0	0	NA	NA	NA	NA
Urine ACR >2000 mg/g, n (%)								
At any visit	0	0	0	0	NA	NA	NA	NA

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
At ≥2 consecutive visits	0	0	0	0	NA	NA	NA	NA
At >1 non-consecutive visits	0	0	0	0	NA	NA	NA	NA
Participants with at least 1 urine sediment measurement, n (%)	425 (74)	188 (66)	341 (60)	174 (61)	NA**	NA**	NA**	NA**
Urine sediment, n (%)								
At any visit	126 (22)	51 (18)	65 (11)	39 (14)	NA	NA	NA	NA
≥5 RBC/HPF	90 (16)	39 (14)	36 (6)	27 (9)	NA	NA	NA	NA
≥5 WBC/HPF	70 (12)	24 (8)	45 (8)	20 (7)	NA	NA	NA	NA
RBC casts	0	0	0	0	NA	NA	NA	NA
WBC casts	0	0	0	0	NA	NA	NA	NA

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	**Placebo N=285**	**Bepirovirsen N=571**	**Placebo N=285**	**Bepirovirsen N=571**	**Placebo N=285**	**Bepirovirsen N=571**	**Placebo N=285**
Hepatobiliary laboratory abnormalities								
Participants with at least 1 post baseline ALT and BIL measurement, n (%)	564 (99)	281 (99)	547 (96)	262 (92)	136 (24)	0	407 (71)	256 (90)
ALT ≥3xULN and BIL ≥2xULN*, n (%)	1 (<1)	0	0	0	0	0	0	0
Participants with at least 1 post baseline ALT, BIL and ALP measurement, n (%)	564 (99)	281 (99)	547 (96)	262 (92)	136 (24)	0	407 (71)	256 (90)
ALT ≥3xULN and BIL ≥2xULN and ALP <2xULN, n (%)	1 (<1)	0	0	0	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
Participants with at least 1 post baseline ALT and INR measurement, n (%)	245 (43)	100 (35)	20 (4)	7 (2)	1 (<1)	0	1 (<1)	1 (<1)
ALT ≥3xULN and INR >1.5†, n (%)	0	0	0	0	0	0	0	0
Hepatocellular injury: Participants with at least 1 post baseline ALT and ALP measurement on the same day, n (%)	564 (99)	281 (99)	547 (96)	262 (92)	136 (24)	0	407 (71)	256 (90)
Hepatocellular injury‡, n (%)	120 (21)	0	2 (<1)	0	0	0	2 (<1)	0
Hepatocellular injury and BIL: Participants with at least 1 post baseline ALT and ALP measurement on	564 (99)	281 (99)	547 (96)	262 (92)	136 (24)	0	407 (71)	256 (90)

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
the same day and at least 1 BIL measurement, n (%)								
Hepatocellular injury‡ and BIL ≥2xULN, n (%)	1 (<1)	0	0	0	0	0	0	0
Participants with at least 1 post baseline ALT measurement, n (%)	564 (99)	281 (99)	547 (96)	262 (92)	136 (24)	0	407 (71)	256 (90)
ALT ≥3xULN, n (%)	142 (25)	0	5 (<1)	0	0	0	2 (<1)	0
ALT ≥5xULN, n (%)	79 (14)	0	2 (<1)	0	0	0	2 (<1)	0
ALT ≥8xULN, n (%)	49 (9)	0	1 (<1)	0	0	0	2 (<1)	0
ALT ≥10xULN, n (%)	37 (7)	0	1 (<1)	0	0	0	1 (<1)	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285
ALT ≥20xULN, n (%)	11 (2)	0	0	0	0	0	0	0

C. Pooled safety population

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Hematological laboratory abnormalities								
Participants with at least 1 post baseline platelet measurement, n (%)	1203 (98)	604 (99)	1168 (96)	563 (92)	289 (24)	0	856 (70)	539 (88)

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**
Platelets <100x10^9/L, n (%)								
At any visit	100 (8)	3 (<1)	53 (4)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)
At ≥2 consecutive visits	33 (3)	1 (<1)	10 (<1)	1 (<1)	0	0	1 (<1)	0
At >1 non-consecutive visits	36 (3)	0	3 (<1)	0	0	0	0	0
Platelets <75x10^9/L, n (%)								
At any visit	17 (1)	1 (<1)	6 (<1)	1 (<1)	0	0	0	0
At ≥2 consecutive visits	5 (<1)	0	0	1 (<1)	0	0	0	0
At >1 non-consecutive visits	3 (<1)	1 (<1)	0	0	0	0	0	0
Platelets <50x10^9/L, n (%)								
At any visit	2 (<1)	0	0	0	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**
At ≥2 consecutive visits	0	0	0	0	0	0	0	0
At >1 non-consecutive visits	0	0	0	0	0	0	0	0
Renal laboratory abnormalities								
Participants with at least 1 post baseline serum creatinine measurement, n (%)	1210 (99)	606 (>99)	1170 (96)	564 (92)	294 (24)	0	861 (70)	546 (89)
Serum creatinine >0.3 mg/dL change from baseline, n (%)								
At any visit	219 (18)	45 (7)	111 (9)	21 (3)	10 (<1)	0	10 (<1)	6 (<1)
At ≥2 consecutive visits	53 (4)	11 (2)	21 (2)	1 (<1)	1 (<1)	0	2 (<1)	0
At >1 non-consecutive visits	73 (6)	11 (2)	20 (2)	1 (<1)	2 (<1)	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Serum creatinine >0.5 mg/dL change from baseline, n (%)								
At any visit	31 (3)	9 (1)	11 (<1)	4 (<1)	1 (<1)	0	1 (<1)	1 (<1)
At ≥2 consecutive visits	4 (<1)	2 (<1)	2 (<1)	0	1 (<1)	0	0	0
At >1 non-consecutive visits	5 (<1)	0	1 (<1)	1 (<1)	0	0	0	0
Participants with at least 1 post baseline eGFR measurement, n (%)	1210 (99)	606 (>99)	1170 (96)	564 (92)	294 (24)	0	861 (70)	546 (89)
eGFR >30% reduction from baseline, n (%)								
At any visit	194 (16)	39 (6)	94 (8)	11 (2)	7 (<1)	0	8 (<1)	6 (<1)
At ≥2 consecutive visits	51 (4)	7 (1)	21 (2)	2 (<1)	1 (<1)	0	0	0
At >1 non-consecutive visits	78 (6)	5 (<1)	26 (2)	0	1 (<1)	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**
eGFR >50% reduction from baseline, n (%)								
At any visit	14 (1)	5 (<1)	3 (<1)	2 (<1)	0	0	1 (<1)	1 (<1)
At ≥2 consecutive visits	1 (<1)	2 (<1)	0	0	0	0	0	0
At >1 non-consecutive visits	1 (<1)	0	0	0	0	0	0	0
Participants with at least 1 post baseline urine ACR measurement, n (%)	1204 (98)	604 (99)	1170 (96)	563 (92)	NA**	NA**	NA**	NA**
Urine ACR >300 mg/g, n (%)								
At any visit	18 (1)	7 (1)	13 (1)	6 (<1)	NA	NA	NA	NA
At ≥2 consecutive visits	4 (<1)	1 (<1)	3 (<1)	1 (<1)	NA	NA	NA	NA
At >1 non-consecutive visits	3 (<1)	2 (<1)	1 (<1)	1 (<1)	NA	NA	NA	NA

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Urine ACR >500 mg/g, n (%)								
At any visit	13 (1)	5 (<1)	5 (<1)	2 (<1)	NA	NA	NA	NA
At ≥2 consecutive visits	3 (<1)	0	3 (<1)	0	NA	NA	NA	NA
At >1 non-consecutive visits	2 (<1)	0	1 (<1)	0	NA	NA	NA	NA
Urine ACR >1000 mg/g, n (%)								
At any visit	6 (<1)	2 (<1)	2 (<1)	1 (<1)	NA	NA	NA	NA
At ≥2 consecutive visits	1 (<1)	0	0	0	NA	NA	NA	NA
At >1 non-consecutive visits	1 (<1)	0	0	0	NA	NA	NA	NA
Urine ACR >2000 mg/g, n (%)								
At any visit	2 (<1)	0	0	0	NA	NA	NA	NA

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
At ≥2 consecutive visits	0	0	0	0	NA	NA	NA	NA
At >1 non-consecutive visits	1 (<1)	0	0	0	NA	NA	NA	NA
Urine sediment, n (%)								
Participants with at least 1 urine sediment measurement, n (%)	895 (73)	422 (69)	749 (61)	354 (58)	NA**	NA**	NA**	NA**
At any visit	267 (22)	111 (18)	149 (12)	83 (14)	NA	NA	NA	NA
≥5 RBC/HPF	183 (15)	76 (12)	84 (7)	51 (8)	NA	NA	NA	NA
≥5 WBC/HPF	151 (12)	61 (10)	97 (8)	49 (8)	NA	NA	NA	NA
RBC casts	0	0	0	0	NA	NA	NA	NA
WBC casts	0	0	0	0	NA	NA	NA	NA

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Hepatobiliary laboratory abnormalities								
Participants with at least 1 post baseline ALT and BIL measurement, n (%)	1210 (99)	606 (>99)	1170 (96)	564 (92)	294 (24)	0	861 (70)	546 (89)
ALT ≥3xULN and BIL ≥2xULN*, n (%)	1 (<1)	0	1 (<1)[§]	0	0	0	0	0
Participants with at least 1 post baseline ALT, BIL and ALP measurement, n (%)	1210 (99)	606 (>99)	1170 (96)	564 (92)	294 (24)	0	861 (70)	546 (89)
ALT ≥3xULN and BIL ≥2xULN and ALP <2xULN, n (%)	1 (<1)	0	1 (<1)	0	0	0	0	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
ALT and INR: Participants with at least 1 post baseline ALT and INR measurement, n (%)	499 (41)	205 (34)	42 (3)	19 (3)	2 (<1)	0	1 (<1)	1 (<1)
ALT ≥3xULN and INR >1.5†, n (%)	0	0	0	0	0	0	0	0
Hepatocellular injury: Participants with at least 1 post baseline ALT and ALP measurement on the same day, n (%)	1210 (99)	606 (>99)	1170 (96)	564 (92)	294 (24)	0	861 (70)	546 (89)
Hepatocellular injury‡, n (%)	239 (20)	2 (<1)	5 (<1)	0	0	0	2 (<1)	2 (<1)
Hepatocellular injury and BIL: Participants with at least 1 post baseline ALT and ALP measurement on	1210 (99)	606 (>99	1170 (96)	564 (92)	294 (24)	0	861 (70)	546 (89)

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
the same day and at least 1 BIL measurement, n (%)								
Hepatocellular injury‡ and BIL ≥2xULN, n (%)	1 (<1)	0	0	0	0	0	0	0
Subjects with at least 1 post baseline ALT, n (%)	1210 (99)	606 (>99)	1170 (96)	564 (92)	294 (24)	0	861 (70)	546 (89)
ALT ≥3xULN, n (%)	292 (24)	2 (<1)	11 (<1)	1 (<1)	0	0	2 (<1)	2 (<1)
ALT ≥5xULN, n (%)	167 (14)	1 (<1)	4 (<1)	0	0	0	2 (<1)	0
ALT ≥8xULN, n (%)	100 (8)	1 (<1)	1 (<1)	0	0	0	2 (<1)	0
ALT ≥10xULN, n (%)	74 (6)	1 (<1)	1 (<1)	0	0	0	1 (<1)	0

	Week 1–24		Week 25–48		Week 49–72			
					NA cessation		Continue NA	
	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
ALT ≥20xULN, n (%)	25 (2)	1 (<1)	0	0	0	0	0	0

INR is not routinely tested through the central laboratory as part of the schedule of assessment.

*If direct bilirubin is available, then direct bilirubin as a portion of total bilirubin must be >35% when total bilirubin is ≥2xULN, in order to satisfy the criteria; bilirubin value is on or up to 28 days after ALT value. †INR value is on or up to 28 days after ALT value. ‡Hepatocellular injury is defined as ([ALT/ALT ULN]/[ALP/ALP ULN]) ≥5 and ALT ≥3xULN. ALT and ALP values must occur on the same day. §This participant also experienced a concurrent SAE of bile duct stone in Week 25–48, which was the likely cause for the event and not considered related to treatment. **Urinalysis is not scheduled after Week 48.

ACR, albumin/creatinine ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BIL, bilirubin; eGFR, estimated glomerular filtration rate; HPF, high-power field; INR, international normalized ratio; RBC, red blood cells; ULN, upper limit of normal; WBC, white blood cells.

Table S6. HBeAg and anti-HBe status at Week 24 and Week 72 and functional cure rate

	B-Well 1				B-Well 2			
	Week 24		Week 72		Week 24		Week 72	
HBeAg positive at baseline	**Bepirovirsen N=55**	**Placebo N=28**	**Bepirovirsen N=55**	**Placebo N=28**	**Bepirovirsen N=43**	**Placebo N=26**	**Bepirovirsen N=43**	**Placebo N=26**
Participants with HBeAg measurement	35 (64)	16 (57)	55 (100)	24 (86)	40 (93)	22 (85)	38 (88)	22 (85)
Participants with anti-HBe measurement	55 (100)	25 (89)	55 (100)	24 (86)	40 (93)	22 (85)	38 (88)	22 (85)
HBeAg loss, n (%)*	12 (22)	0	16 (29)	3 (11)	15 (35)	1 (4)	11 (26)	2 (8)
Seroconversion from HBeAg-positive to negative and anti-HBe negative to positive, n (%)[†]	4 (33)	0	3 (19)	1 (33)	4 (27)	0	3 (27)	0

HBeAg loss and functional cure[‡], n (%)*	5 (9)	0	6 (11)	0	1 (2)	0	2 (5)	0
Seroconversion from HBeAg-positive to negative, anti-HBe negative to positive and achieved functional cure, n (%)[†]	2 (40)	0	1 (17)	0	0	0	0	0

*Percentage calculated among those HBeAg-positive at baseline. [†]Percentage calculated among those who converted from HBeAg positive at baseline to negative at the week of interest. [‡]Achieved functional cure at Week 72.

HBeAg, hepatitis B e-antigen.

Table S7. Mean (SD) anti-HBs at baseline and Weeks 24, 48 and 72

	B-Well 1		B-Well 2	
	Bepirovirsen N=650	**Placebo N=328**	**Bepirovirsen N=570**	**Placebo N=286**
Anti-HBs				
Baseline, n	624	311	551	279
mean (SD), IU/L	5.1 (10.8)	4.2 (2.8)	7.4 (64.5)	4.6 (4.8)
Week 24, n	607	296	527	250
mean (SD), IU/L	129.4 (1042.2)	4.8 (9.0)	63.6 (230.5)	4.4 (3.3)
Week 48, n	611	291	537	259
mean (SD), IU/L	55.5 (397.7)	4.5 (4.8)	111.3 (1205.6)	4.6 (4.3)
Week 72, n	602	287	533	250
mean (SD), IU/L	38.2 (190.5)	4.5 (5.0)	128.5 (1536.0)	4.7 (4.7)

Anti-HBs, hepatitis B surface antibody; SD, standard deviation.

Table S8. Participants with adverse events by study stage over Week 1–72

A. B-Well 1

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=652	PBO N=326	BPV N=635	PBO N=314	BPV N=623	PBO N=304	BPV N=457	PBO N=293	BPV N=159	PBO N=0	BPV N=652	PBO N=326
Any AE, n (%)	538 (83)	182 (56)	417 (66)	136 (43)	294 (47)	131 (43)	91 (20)	51 (17)	65 (41)	0	585 (90)	232 (71)
AEs leading to permanent discontinuation of study treatment*	20 (3)	0	6 (<1)	0	0	0	0	0	0	0	26 (4)	0
AEs leading to dose reduction*	12 (2)	0	1 (<1)	0	0	0	0	0	0	0	13 (2)	0

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=652	PBO N=326	BPV N=635	PBO N=314	BPV N=623	PBO N=304	BPV N=457	PBO N=293	BPV N=159	PBO N=0	BPV N=652	PBO N=326
AEs leading to dose interruption/delay*	56 (9)	6 (2)	54 (9)	4 (1)	0	0	0	0	0	0	100 (15)	10 (3)
AEs of Grade ≥3 severity†	82 (13)	5 (2)	18 (3)	4 (1)	19 (3)	7 (2)	4 (<1)	4 (1)	3 (2)	0	113 (17)	18 (6)
AESIs‡, n (%)												
Injection-site reaction	304 (47)	34 (10)	161 (25)	12 (4)	20 (3)	0	2 (<1)	0	0	0	331 (51)	39 (12)
Vascular inflammation, complement	156 (24)	28 (9)	79 (12)	15 (5)	28 (4)	17 (6)	16 (4)	9 (3)	5 (3)	0	236 (36)	56 (17)

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=652	PBO N=326	BPV N=635	PBO N=314	BPV N=623	PBO N=304	BPV N=457	PBO N=293	BPV N=159	PBO N=0	BPV N=652	PBO N=326
activation, and other immune associated effects												
Thrombocytopenia	201 (31)	32 (10)	160 (25)	19 (6)	28 (4)	4 (1)	3 (<1)	3 (1)	1 (<1)	0	281 (43)	47 (14)
ALT increase	176 (27)	14 (4)	34 (5)	8 (3)	16 (3)	8 (3)	8 (2)	4 (1)	4 (3)	0	185 (28)	28 (9)
Renal injury	58 (9)	21 (6)	68 (11)	21 (7)	36 (6)	10 (3)	2 (<1)	2 (<1)	1 (<1)	0	101 (15)	33 (10)
Any SAE, n (%)	16 (2)	4 (1)	9 (1)	2 (<1)	19 (3)	5 (2)	3 (<1)	3 (1)	0	0	47 (7)	11 (3)
SAEs related to study treatment	9 (1)	0	3 (<1)	0	0	0	0	0	0	0	12 (2)	0

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=652	PBO N=326	BPV N=635	PBO N=314	BPV N=623	PBO N=304	BPV N=457	PBO N=293	BPV N=159	PBO N=0	BPV N=652	PBO N=326
Fatal SAEs[§]	0	0	0	0	1 (<1)	0	0	0	0	0	1 (<1)	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0	0	0	0	0

B. B-Well 2

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=571	PBO N=285	BPV N=554	PBO N=272	BPV N=550	PBO N=262	BPV N=409	PBO N=257	BPV N=136	PBO N=0	BPV N=571	PBO N=285
Any AE, n (%)	486 (85)	158 (55)	380 69)	131 (48)	282 (51)	113 (43)	96 (23)	55 (21)	59 (43)	0	525 (92)	212 (74)
AEs leading to permanent discontinuation of study treatment*	11 (2)	2 (<1)	4 (<1)	0	0	0	0	0	0	0	15 (3)	2 (<1)
AEs leading to dose reduction*	11 (2)	0	0	0	0	0	0	0	0	0	11 (2)	0
AEs leading to dose interruption/delay*	59 (10)	2 (<1)	45 (8)	1 (<1)	0	0	0	0	0	0	93 (16)	3 (1)

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=571	PBO N=285	BPV N=554	PBO N=272	BPV N=550	PBO N=262	BPV N=409	PBO N=257	BPV N=136	PBO N=0	BPV N=571	PBO N=285
AEs of Grade ≥3 severity[†]	80 (14)	3 (1)	26 (5)	6 (2)	18 (3)	5 (2)	6 (1)	5 (2)	1 (<1)	0	119 (21)	17 (6)
AESIs[‡], n (%)												
Injection-site reaction	292 (51)	32 (11)	163 (29)	23 (8)	25 (5)	1 (<1)	1 (<1)	0	0	0	321 (56)	45 (16)
Vascular inflammation, complement activation, and other immune associated effects	153 (27)	28 (10)	86 (16)	10 (4)	32 (6)	12 (5)	13 (3)	7 (3)	11 (8)	0	217 (38)	47 (16)
Thrombocytopenia	186 (33)	28 (10)	146 (26)	21 (8)	20 (4)	5 (2)	5 (1)	0	2 (1)	0	238 (42)	42 (15)
ALT increase	150 (26)	9 (3)	47 (8)	7 (3)	41 (7)	9 (3)	10 (2)	3 (1)	3 (2)	0	175 (31)	22 (8)

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=571	PBO N=285	BPV N=554	PBO N=272	BPV N=550	PBO N=262	BPV N=409	PBO N=257	BPV N=136	PBO N=0	BPV N=571	PBO N=285
Renal injury	76 (13)	14 (5)	83 (15)	23 (8)	64 (12)	14 (5)	3 (<1)	1 (<1)	8 (6)	0	118 (21)	32 (11)
Any SAE, n (%)	18(3)	0	5 (<1)	3 (1)	13 (2)	7 (3)	7 (2)	5 (2)	0	0	45 (8)	14 (5)
SAEs related to study treatment	10 (2)	0	1 (<1)	0	1 (<1)	0	0	0	0	0	12 (2)	0
Fatal SAEs[§]	1 (<1)	0	0	0	0	0	0	0	0	0	1 (<1)	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0	0	0	0	0

C. Pooled safety population

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=1223	PBO N=611	BPV N=1189	PBO N=586	BPV N=1173	PBO N=566	BPV N=866	PBO N=550	BPV N=295	PBO N=0	BPV N=1223	PBO N=611
Any AE, n (%)	1024 (84)	340 (56)	797 (67)	267 (46)	576 (49)	244 (43)	187 (22)	106 (19)	124 (42)	0	1109 (91)	444 (73)
AEs leading to permanent discontinuation of study treatment*	31 (3)	2 (<1)	10 (<1)	0	0	0	0	0	0	0	41 (3)	2 (<1)
AEs leading to dose reduction*	23 (2)	0	1 (<1)	0	0	0	0	0	0	0	24 (2)	0
AEs leading to dose interruption/delay*	115 (9)	8 (1)	99 (8)	5 (<1)	0	0	0	0	0	0	193 (16)	13 (2)

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=1223	PBO N=611	BPV N=1189	PBO N=586	BPV N=1173	PBO N=566	BPV N=866	PBO N=550	BPV N=295	PBO N=0	BPV N=1223	PBO N=611
AEs of Grade ≥3 severity[†]	162 (13)	8 (1)	44 (4)	10 (2)	37 (3)	12 (2)	10 (1)	9 (2)	4 (1)	0	231 (19)	35 (6)
AESIs[‡], n (%)												
Injection-site reaction	596 (49)	66 (11)	324 (27)	35 (6)	45 (4)	1 (<1)	3 (<1)	0	0	0	652 (53)	84 (14)
Vascular inflammation, complement activation, and other immune associated effects	309 (25)	56 (9)	165 (14)	25 (4)	60 (5)	29 (5)	29 (3)	16(3)	16 (5)	0	450 (37)	103 (17)
Thrombocytopenia	387 (32)	60 (10)	306 (26)	40 (7)	48 (4)	9 (2)	8 (<1)	3 (<1)	3 (1)	0	519 (42)	89 (15)
ALT increase	326 (27)	23 (4)	81 (7)	15 (3)	57 (5)	17 (3)	18 (2)	7 (1)	7 (2)	0	360 (29)	50 (8)

	Treatment period				Post study treatment						Overall	
	Week 1–12		Week 13–24		Week 25–48		Week 49–72 NA continued		Week 49–72 NA discontinued		Week 1–72	
	BPV N=1223	PBO N=611	BPV N=1189	PBO N=586	BPV N=1173	PBO N=566	BPV N=866	PBO N=550	BPV N=295	PBO N=0	BPV N=1223	PBO N=611
Renal injury	134 (11)	35 (6)	151 (13)	44 (8)	100 (9)	24 (4)	5 (<1)	3 (<1)	9 (3)	0	218 (18)	65 (11)
Any SAE, n (%)	34 (3)	4 (<1)	14 (1)	5 (<1)	32 (3)	12 (2)	10 (1)	8 (1)	0	0	88 (7)	25 (4)
SAEs related to study treatment	19 (2)	0	4 (<1)	0	1 (<1)	0	0	0	0	0	24 (2)	0
Fatal SAEs‡	1 (<1)	0	0	0	1 (<1)	0	0	0	0	0	2 (<1)	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0	0	0	0	0

D. Participants with adverse events of special interest during the treatment period (Week1–24), in B-Well 1, B-Well 2, and both studies pooled

	B-Well 1		B-Well 2		Pooled data	
	BPV N=652	**PBO N=326**	**BPV N=571**	**PBO N=285**	**BPV N=1223**	**PBO N=611**
Any AE, n (%)	575 (88)	210 (64)	512 (90)	189 (66)	1087 (89)	399 (65)
AESIs[‡], n (%)						
Injection-site reactions	330 (51)	39 (12)	318 (56)	45 (16)	648 (53)	84 (14)
Vascular inflammation, complement activation, and other immune associated effects	207 (32)	40 (12)	194 (34)	32 (11)	401 (33)	72 (12)
Thrombocytopenia	274 (42)	43 (13)	235 (41)	41 (14)	509 (42)	84 (14)
ALT increase	183 (28)	20 (6)	160 (28)	14 (5)	343 (28)	34 (6)
Renal injury	90 (14)	29 (9)	106 (19)	28 (10)	196 (16)	57 (9)

*AE categories were not mutually exclusive; participants may have been counted in more than one category. [†]AEs were graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1. Grade 1 indicates a mild event, Grade 2 a moderate event, Grade 3 a severe event, Grade 4 a potentially life-threatening event, and Grade 5 death. Investigators judgement may be used in assigning clinical severity, and may not always align with DAIDS grading. [‡]AESIs are subset of events reported as AEs; events are reported under both headings. AESIs were defined according to standardized *Medical Dictionary for Regulatory Activities* (MedDRA) queries or MedDRA high-level terms or individual Preferred Terms (see **Table S12** for further information). [§]A death in B-Well 1 occurred

following a reported “near drowning” event during Weeks 37–48, ten months after the last dose of study treatment. The death in B-Well 2 was aortic dissection 25 days after study treatment initiation, with autopsy findings indicative of cardiovascular disease.

Participants may be listed in more than one stage.
AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; BPV, bepirovirsen; PBO, placebo; SAE, serious adverse event.

Table S9. Adverse events (Week 1–24; treatment period) reported in ≥3% of participants across treatment arms in the pooled safety population by Preferred Term

	B-Well 1		B-Well 2		Pooled safety population	
	Bepirovirsen N=652	**Placebo N=326**	**Bepirovirsen N=571**	**Placebo N=285**	**Bepirovirsen N=1223**	**Placebo N=611**
Injection site erythema	196 (30)	6 (2)	188 (33)	6 (2)	384 (31)	12 (2)
Injection site pain	130 (20)	13 (4)	147 (26)	18 (6)	277 (23)	31 (5)
Alanine aminotransferase increased	148 (23)	13 (4)	121 (21)	5 (2)	269 (22)	18 (3)
Pyrexia	132 (20)	10 (3)	104 (18)	8 (3)	236 (19)	18 (3)
Headache	93 (14)	35 (11)	75 (13)	35 (12)	168 (14)	70 (11)
Injection site pruritus	104 (16)	6 (2)	115 (20)	3 (1)	219 (18)	9 (1)
Upper respiratory tract infection	71 (11)	39 (12)	76 (13)	33 (12)	147 (12)	72 (12)
Injection site bruising	81 (12)	12 (4)	95 (17)	16 (6)	176 (14)	28 (5)
Aspartate aminotransferase increased	96 (15)	5 (2)	87 (15)	3 (1)	183 (15)	8 (1)

	B-Well 1		B-Well 2		Pooled safety population	
	Bepirovirsen N=652	**Placebo N=326**	**Bepirovirsen N=571**	**Placebo N=285**	**Bepirovirsen N=1223**	**Placebo N=611**
Platelet count decreased	97 (15)	2 (<1)	83 (15)	3 (1)	180 (15)	5 (<1)
Fatigue	63 (10)	16 (5)	50 (9)	13 (5)	113 (9)	29 (5)
Nasopharyngitis	41 (6)	29 (9)	30 (5)	19 (7)	71 (6)	48 (8)
Myalgia	51 (8)	11 (3)	44 (8)	8 (3)	95 (8)	19 (3)
Thrombocytopenia	55 (8)	6 (2)	45 (8)	4 (1)	100 (8)	10 (2)
Injection site swelling	40 (6)	1 (<1)	53 (9)	1 (<1)	93 (8)	2 (<1)
Injection site discoloration	45 (7)	2 (<1)	38 (7)	1 (<1)	83 (7)	3 (<1)
Glomerular filtration rate decreased	27 (4)	9 (3)	39 (7)	4 (1)	66 (5)	13 (2)
Injection site reaction	41 (6)	0	36 (6)	2 (<1)	77 (6)	2 (<1)
Cough	34 (5)	16 (5)	20 (4)	8 (3)	54 (4)	24 (4)
Diarrhea	26 (4)	21 (6)	20 (4)	6 (2)	46 (4)	27 (4)

	B-Well 1		B-Well 2		Pooled safety population	
	Bepirovirsen N=652	**Placebo N=326**	**Bepirovirsen N=571**	**Placebo N=285**	**Bepirovirsen N=1223**	**Placebo N=611**
Protein urine present	27 (4)	9 (3)	25 (4)	10 (4)	52 (4)	19 (3)
Pruritus	34 (5)	5 (2)	22 (4)	7 (2)	56 (5)	12 (2)
Arthralgia	29 (4)	10 (3)	20 (4)	7 (2)	49 (4)	17 (3)
Erythema	26 (4)	1 (<1)	36 (6)	2 (<1)	62 (5)	3 (<1)
Back pain	22 (3)	12 (4)	19 (3)	11 (4)	41 (3)	23 (4)
Dizziness	23 (4)	9 (3)	21 (4)	11 (4)	44 (4)	20 (3)
Injection site hemorrhage	34 (5)	2 (<1)	22 (4)	5 (2)	56 (5)	7 (1)
Asthenia	30 (5)	1 (<1)	26 (5)	4 (1)	56 (5)	5 (<1)
Influenza-like illness	21 (3)	5 (2)	26 (5)	4 (1)	47 (4)	9 (1)

Table S10. SAEs and SAEs related to study treatment by System Organ Class and Preferred Term (Weeks 1–24; treatment period)

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Any SAE, n (%)	**25 (4)**	**5 (2)**	**12 (2)**	**0**	**23 (4)**	**3 (1)**	**11 (2)**	**0**	**48 (4)**	**8 (1)**	**23 (2)**	**0**
Infections and infestations	**3 (<1)**	**1 (<1)**	**0**	**0**	**7 (1)**	**0**	**1 (<1)**	**0**	**10 (<1)**	**1 (<1)**	**1 (<1)**	**0**
Gastroenteritis	1 (<1)	0	0	0	1 (<1)	0	1 (<1)	0	2 (<1)	0	1 (<1)	0
Pneumonia	0	1 (<1)	0	0	1 (<1)	0	0	0	1 (<1)	1 (<1)	0	0
Abscess limb	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Appendicitis	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Chronic sinusitis	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Dengue fever	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Endocarditis	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Herpes zoster	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Urinary tract infection	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Hepatobiliary disorders	**3 (<1)**	**0**	**2 (<1)**	**0**	**5 (<1)**	**0**	**5 (<1)**	**0**	**8 (<1)**	**0**	**7 (<1)**	**0**
Immune-mediated hepatic disorder†	0	0	0	0	4 (<1)	0	4 (<1)	0	4 (<1)	0	4 (<1)	0
Hepatic function abnormal†	2 (<1)	0	2 (<1)	0	1 (<1)	0	1 (<1)	0	3 (<1)	0	3 (<1)	0
Bile duct stone	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Injury, poisoning and procedural complications	**1 (<1)**	**1 (<1)**	**0**	**0**	**3 (<1)**	**1 (<1)**	**0**	**0**	**4 (<1)**	**2 (<1)**	**0**	**0**
Burns second degree	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Craniofacial fracture	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Fall	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0
Lower limb fracture	0	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Multiple injuries	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Subdural hemorrhage	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Upper limb fracture	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
General disorders and administration site conditions	**2 (<1)**	**0**	**1 (<1)**	**0**	**2 (<1)**	**0**	**0**	**0**	**4 (<1)**	**0**	**1 (<1)**	**0**
Chest pain	2 (<1)	0	1 (<1)	0	0	0	0	0	2 (<1)	0	1 (<1)	0
Asthenia	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Death	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Musculoskeletal and connective tissue disorders	**1 (<1)**	**2 (<1)**	**0**	**0**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**3 (<1)**	0	0
Arthralgia	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Intervertebral disc protrusion	0	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Myalgia	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Rotator cuff syndrome	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**4 (<1)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**4 (<1)**	**0**	**0**	**0**
B-cell lymphoma	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Extramammary Paget's disease	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Neoplasm prostate	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Pancreatic neoplasm‡	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Renal and urinary disorders	**1 (<1)**	**1 (<1)**	**0**	**0**	**2 (<1)**	**0**	**1 (<1)**	**0**	**3 (<1)**	**1 (<1)**	**1 (<1)**	**0**
Hydronephrosis	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
IgA nephropathy	0	0	0	0	1 (<1)	0	1 (<1)	0	1 (<1)	0	1 (<1)	0
Renal colic	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Renal impairment	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Gastrointestinal disorders	**2 (<1)**	**1 (<1)**	**2 (<1)**	**0**	**0**	**0**	**0**	**0**	**2 (<1)**	**1 (<1)**	**2 (<1)**	**0**
Inguinal hernia	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0
Omental infarction	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1)	0	1 (<1)	0
Vomiting	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1)	0	1 (<1)	0
Investigations	**2 (<1)**	**0**	**2 (<1)**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**	**3 (<1)**	**0**	**3 (<1)**	**0**
Alanine aminotransferase increased	0	0	0	0	1 (<1)	0	1 (<1)	0	1 (<1)	0	1 (<1)	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Aspartate aminotransferase increased	0	0	0	0	1 (<1)	0	1 (<1)	0	1 (<1)	0	1 (<1)	0
Coagulation factor decreased	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1)	0	1 (<1)	0
Platelet count decreased	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1)	0	1 (<1)	0
Nervous system disorders	**3 (<1)**	**0**	**2 (<1)**	**0**	**0**	**0**	**0**	**0**	**3 (<1)**	**0**	**2 (<1)**	**0**
Presyncope	2 (<1)	0	1 (<1)	0	0	0	0	0	2 (<1)	0	1 (<1)	0
Myoclonus	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1)	0	1 (<1)	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Blood and lymphatic system disorders	**2 (<1)**	**0**	**2 (<1)**	**0**	**0**	**0**	**0**	**0**	**2 (<1)**	**0**	**2 (<1)**	**0**
Autoimmune hemolytic anemia	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1)	0	1 (<1)	0
Thrombocytopenia	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1)	0	1 (<1)	0
Eye disorders	**1 (<1)**	**0**	**0**	**0**	**0**	**1 (<1)**	**0**	**0**	**1 (<1)**	**1 (<1)**	**0**	**0**
Cataract	0	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Epiretinal membrane	0	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Optic atrophy	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Cardiac disorders	**0**	**0**	**0**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Tachycardia	0	0	0	0	1 (<1)	0	1 (<1)	0	1 (<1)	0	1 (<1)	0
Ear and labyrinth disorders	**1 (<1)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (<1)**	**0**	**0**	**0**
Endolymphatic hydrops	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0	0	0
Psychiatric disorders	**0**	**0**	**0**	**0**	**1 (<1)**	**0**	**0**	**0**	**1 (<1)**	**0**	**0**	**0**
Suicide attempt	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0
Reproductive system and breast disorders	**0**	**0**	**0**	**0**	**1 (<1)**	**0**	**0**	**0**	**1 (<1)**	**0**	**0**	**0**
Breast disorder	0	0	0	0	1 (<1)	0	0	0	1 (<1)	0	0	0

	B-Well 1				B-Well 2				Pooled safety population			
	SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*		SAEs in Week 1–24		Treatment-related SAEs in Week 1–24*	
	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=652	Placebo N=326	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=571	Placebo N=285	Bepirovirsen N=1223	Placebo N=611	Bepirovirsen N=1223	Placebo N=611
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**
Lung disorder	0	0	0	0	1 (<1)	0	1 (<1)	0	1 (<1)	0	1 (<1)	0
Skin and subcutaneous tissue disorders	**1 (<1)**	**0**	**1 (<1)**	**0**	**0**	**0**	**0**	**0**	**1 (<1%)**	**0**	**1 (<1%)**	**0**
Cutaneous vasculitis	1 (<1)	0	1 (<1)	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0
Vascular disorders	**0**	**0**	**0**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**	**1 (<1%)**	**0**	**1 (<1%)**	**0**
Vasculitis	0	0	0	0	1 (<1)	0	1 (<1)	0	1 (<1%)	0	1 (<1%)	0

*SAEs related to study treatment are a subcategory of SAEs; events are recorded in both. [†]'Immune-mediated hepatic disorder' and 'Hepatic function abnormal' described ALT increases (with/without bilirubin increase) and were captured under different Preferred Terms due to physician's discretion in SAE reporting. [‡]A death occurred after study withdrawal of the participant who had an SAE of pancreatic neoplasm during the study.

ALT, alanine aminotransferase; IgA, immunoglobulin A; SAE, serious adverse event.

Table S11. Summary of protocol-defined treatment hold or stopping events (Week 1–24)

A. B-Well 1

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=652	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**
Hematological treatment holding/stopping events*						
Participants with hematological holding/stopping events, n (%)	17 (3)	1 (<1)	58 (9)	1 (<1)	63 (10)	2 (<1)
Participants with hematological stopping events, n (%)	2 (<1)	1 (<1)	2 (<1)	0	4 (<1)	1 (<1)
Platelet count 50 x 10^9/L to <75 x 10^9/L and positive for anti-platelet antibodies, n/N (%)	0/2	1/1 (100)	2/2 (100)	0	2/4 (50)	1/1 (100)
Platelet count <50 x 10^9/L, n/N (%)	2/2 (100)	0/1	0/2	0	2/4 (50)	0/1
Participants with hematological hold event, n (%)	15 (2)	0	57 (9)	1 (<1)	60 (9)	1 (<1)
Platelet count 75 x 10^9/L to <100 x 10^9/L, n/N (%)	15/15 (100)	0	54//57 (95)	1/1 (100)	57/60 (95)	1/1 (100)
Platelet count 50 x 10^9/L to <75 x 10^9/L and negative for anti-platelet antibodies, n/N (%)	0/15	0	3/57 (5)	0/1	3/60 (5)	0/1
Drug-induced kidney (renal) injury treatment holding/stopping events						
Participants with drug-induced kidney injury holding/stopping event, n (%)	6 (<1)	2 (<1)	18 (3)	1 (<1)	22 (3)	3 (<1)

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=652	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**
Participants with drug-induced kidney injury stopping event, n (%)	0	0	0	0	0	0
uACR ≥2 mg/mg (2000 mg/g) and acute glomerulonephritis is confirmed or probable, n/N (%)	0	0	0	0	0	0
Participants with drug-induced kidney injury hold event, n (%)	6 (<1)	2 (<1)	18 (3)	1 (<1)	22 (3)	3 (<1)
uACR ≥0.5 mg/mg (≥500 mg/g) for 2 or more consecutive weeks, n/N (%)	2/6 (33)	1/2 (50)	5/18 (28)	0/1	7/22 (32)	1/3 (33)
eGFR >30% reduction from pre-dose range for 2 or more consecutive weeks, n/N (%)	3/6 (50)	1/2 (50)	15/18 (83)	1/1 (100)	17/22 (77)	2/3 (67)
uACR ≥2 mg/mg (2000 mg/g) and acute glomerulonephritis is not confirmed or probable, n/N (%)	2/6 (33)	0/2	1/18 (6)	0/1	3/22 (14)	0/3
Liver monitoring[†]/treatment holding/stopping event						
Participants with liver monitoring/holding/stopping events, n (%)	40 (6)	1 (<1)	0	0	40 (6)	1 (<1)
Participants with liver stopping events, n (%)	1 (<1)	0	0	0	1 (<1)	0
Participants with liver holding event that never reached stopping criteria, n (%)	26 (4)	1 (<1)	0	0	26 (4)	1 (<1)
Participants with liver monitoring event that never reached holding/stopping criteria, n (%)	13 (2)	0	0	0	13 (2)	0
Potential drug-induced vascular injury and complement holding/stopping events[‡]						
Participants with drug-induced vascular injury and complement holding/stopping events, n (%)	5 (<1)	0	2 (<1)	0	7 (1)	0

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=652	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**	**Bepirovirsen N=652**	**Placebo N=326**
Participants with drug-induced vascular injury and treatment stopping event, n (%)	5 (<1)	0	1 (<1)	0	6 (<1)	0
Suspected clinical sequelae of complement activation, drug induced vascular injury, vasculitis or auto immunity regardless of biomarkers changes or persistence, n/N (%)	5/5 (100)	0	1/1 (100)	0	6/6 (100)	0
Participants with drug-induced vascular injury and treatment hold event, n (%)	0	0	1 (<1)	0	1 (<1)	0
Developed signs/symptoms of potential complement activation/drug-induced vascular injury, n/N (%)	0	0	1/1 (100)	0	1/1 (100)	0

B. B-Well 2

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=571	**Placebo N=3285**	**Bepirovirsen N=571**	**Placebo N=285**	**Bepirovirsen N=571**	**Placebo N=285**
Hematological treatment holding/stopping events*						
Participants with hematological holding/stopping events, n (%)	12 (2)	1 (<1)	54 (9)	1 (<1)	57 (10)	2 (<1)
Participants with hematological stopping events, n (%)	0	0	4 (<1)	0	4 (<1)	0
Platelet count 50 x 10^9/L to <75 x 10^9/L and positive for anti-platelet antibodies, n/N (%)	0	0	4/4 (100)	0	4/4 (100)	0
Platelet count <50 x 10^9/L, n/N (%)	0	0	0/4	0	0/4	0
Participants with hematological hold event, n (%)	12 (2)	1 (<1)	51 (9)	1 (<1)	54 (9)	2 (<1)
Platelet count 75 x 10^9/L to <100 x 10^9/L, n/N (%)	11/12 (92)	1/1 (100)	45/51 (88)	1/1 (100)	49/54 (91)	2/2 (100)
Platelet count 50 x 10^9/L to <75 x 10^9/L and negative for anti-platelet antibodies, n/N (%)	1/12 (8)	0/1	6/51 (12)	0/1	5/54 (9)	0/2
Drug-induced kidney (renal) injury treatment holding/stopping events						
Participants with drug-induced kidney injury holding/stopping event, n (%)	3 (<1)	1 (<1)	11 (2)	0	13 (2)	1 (<1)
Participants with drug-induced kidney injury stopping event, n (%)	0	0	0	0	0	0

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=571	**Placebo N=3285**	**Bepirovirsen N=571**	**Placebo N=285**	**Bepirovirsen N=571**	**Placebo N=285**
uACR ≥2 mg/mg (2000 mg/g) and acute glomerulonephritis is confirmed or probable, n/N (%)	0	0	0	0	0	0
Participants with drug-induced kidney injury hold event, n (%)	3 (<1)	1 (<1)	11 (2)	0	13 (2)	1 (<1)
uACR ≥0.5 mg/mg (≥500 mg/g) for 2 or more consecutive weeks, n/N (%)	2/3 (67)	0/1	1/11 (9)	0	3/13 (23)	0/1
eGFR >30% reduction from pre-dose range for 2 or more consecutive weeks, n/N (%)	2/3 (67)	1/1 (100)	10/11 (91)	0	11/13 (85)	1/1 (100)
uACR ≥2 mg/mg (2000 mg/g) and acute glomerulonephritis is not confirmed or probable, n/N (%)	0/3	0/1	0/11	0	0/13	0/1
Liver monitoring[†]/treatment holding/stopping event						
Participants with liver monitoring/holding/stopping events, n (%)	36 (6)	0	0	0	36 (6)	0
Participants with liver stopping events, n (%)	3 (<1)	0	0	0	3 (<1)	0
Participants with liver holding event that never reached stopping criteria, n (%)	27 (5)	0	0	0	27 (5)	0
Participants with liver monitoring event that never reached holding/stopping criteria, n (%)	6 (1)	0	0	0	6 (1)	0
Potential drug-induced vascular injury and complement holding/stopping events[‡]						
Participants with drug-induced vascular injury and complement holding/stopping events, n (%)	3 (<1)	0	0	0	3 (<1)	0
Participants with drug-induced vascular injury and treatment stopping event, n (%)	3 (<1)	0	0	0	3 (<1)	0

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=571	**Placebo N=3285**	**Bepirovirsen N=571**	**Placebo N=285**	**Bepirovirsen N=571**	**Placebo N=285**
Suspected clinical sequelae of complement activation, drug induced vascular injury, vasculitis or auto immunity regardless of biomarkers changes or persistence, n/N (%)	3/3 (100)	0	0	0	3/3 (100)	0
Participants with drug-induced vascular injury and treatment hold event, n (%)	0	0	0	0	0	0
Developed signs/symptoms of potential complement activation/drug-induced vascular injury, n/N (%)	0	0	0	0	0	0

C. Pooled safety population

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=1223	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**
Hematological treatment holding/stopping events*						
Participants with hematological holding/stopping events, n (%)	29 (2)	2 (<1)	112 (9)	2 (<1)	120 (10)	4 (<1)
Participants with hematological stopping events, n (%)	2 (<1)	1 (<1)	6 (<1)	0	8 (<1)	1 (<1)
Platelet count 50 x 10^9/L to <75 x 10^9/L and positive for anti-platelet antibodies, n/N (%)	0/2	1/1 (100)	6/6 (100)	0	6/8 (75)	1/1 (100)
Platelet count <50 x 10^9/L, n/N (%)	2/2 (100)	0/1	0/6	0	2/8 (25)	0/1
Participants with hematological hold event, n (%)	27 (2)	1 (<1)	108 (9)	2 (<1)	114 (9)	3 (<1)
Platelet count 75 x 10^9/L to <100 x 10^9/L, n/N (%)	26/27 (96)	1/1 (100)	99/108 (92)	2/2 (100)	106/114 (93)	3/3 (100)
Platelet count 50 x 10^9/L to <75 x 10^9/L and negative for anti-platelet antibodies, n/N (%)	1/27 (4)	0/1	9/108 (8)	0/2	8/114 (7)	0/3
Drug-induced kidney (renal) injury treatment holding/stopping events						
Participants with drug-induced kidney injury holding/stopping event, n (%)	9 (<1)	3 (<1)	29 (2)	1 (<1)	35 (3)	4 (<1)
Participants with drug-induced kidney injury stopping event, n (%)	0	0	0	0	0	0

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=1223	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**
uACR ≥2 mg/mg (2000 mg/g) and acute glomerulonephritis is confirmed or probable, n/N (%)	0	0	0	1 (<1)	0	0
Participants with drug-induced kidney injury hold event, n (%)	9 (<1)	3 (<1)	29 (2)	1 (<1)	35 (3)	4 (<1)
uACR ≥0.5 mg/mg (≥500 mg/g) for 2 or more consecutive weeks, n/N (%)	4/9 (44)	1/3 (33)	6/29 (21)	0/1	10/35 (29)	1/4 (25)
eGFR >30% reduction from pre-dose range for 2 or more consecutive weeks, n/N (%)	5/9 (56)	2/3 (67)	25/29 (86)	1/1 (100)	28/35 (80)	3/4 (75)
uACR ≥2 mg/mg (2000 mg/g) and acute glomerulonephritis is not confirmed or probable, n/N (%)	2/9 (22)	0/3	1/29 (3)	0/1	3/35 (9)	0/4
Liver monitoring[†]/treatment holding/stopping event						
Participants with liver monitoring/holding/stopping events, n (%)	76 (6)	1 (<1)	0	0	76 (6)	1 (<1)
Participants with liver stopping events, n (%)	4 (<1)	0	0	0	4 (<1)	0
Participants with liver holding event that never reached stopping criteria, n (%)	53 (4)	1 (<1)	0	0	53 (4)	1 (<1)
Participants with liver monitoring event that never reached holding/stopping criteria, n (%)	19 (2)	0	0	0	19 (2)	0
Potential drug-induced vascular injury and complement holding/stopping events[‡]						
Participants with drug-induced vascular injury and complement holding/stopping events, n (%)	8 (<1)	0	2 (<1)	0	10 (<1)	0
Participants with drug-induced vascular injury and treatment stopping event, n (%)	8 (<1)	0	1 (<1)	0	9 (<1)	0

	Week 1–12		Week 13–24		Week 1–24	
	Bepirovirsen N=1223	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**	**Bepirovirsen N=1223**	**Placebo N=611**
Suspected clinical sequelae of complement activation, drug induced vascular injury, vasculitis or auto immunity regardless of biomarkers changes or persistence, n/N (%)	8/ 8 (100)	0	1/1 (100)	0	9/9 (100)	0
Participants with drug-induced vascular injury and treatment hold event, n (%)	0	0	1 (<1)	0	1 (<1)	0
Developed signs/symptoms of potential complement activation/drug-induced vascular injury, n/N (%)	0	0	1/1 (100)	0	1/1 (100)	0

*Holding/stopping events are derived from lab assessment. Holding event is defined as participant meeting predefined criteria that trigger treatment hold until resolution without triggering permanent discontinuation. Participants can have >1 on-hold event. For participants with >1 event, the earliest most severe criteria event is summarized. Stopping event is defined as when participant meets predefined criteria that trigger discontinuation of study treatment and additional actions and follow-up assessments. †Liver monitoring event is when participant meets predefined liver chemistry monitoring criteria that trigger increased monitoring of liver chemistries and may or may not include a temporary hold. Liver stopping event is when participant meets predefined liver chemistry stopping criteria that trigger discontinuation of study treatment and requirement of additional actions and follow-up assessments to be performed. For participants with >1 stopping or monitoring event, only data related to the earliest most severe criteria event is included. ‡Events generally manifested as cutaneous vasculitis, with skin purpuric rash with or without joint pain.

eGFR, estimated glomerular filtration rate; uACR, urine albumin-to-creatinine ratio.

Table S12. MedDRA SMQ, HLT or selected individual PTs used to define AESI and closely monitored events*

AESI name	**Group of terms** **(MedDRA SMQ, HLT or individual PTs)**	**Comment**
ALT increase	• Drug related hepatic disorders – comprehensive search (SMQ) (*Broad)* • PT: Hepatitis B	Drug-related hepatic disorders is a sub-SMQ of hepatic disorders SMQ
Vascular inflammation, complement activation and other immune-associated effects	• Vasculitis SMQ (Broad) • Hypersensitivity SMQ (Broad) • Immune response protein analyses NEC (HLT) • Immune-mediated/autoimmune disorders (SMQ)	

Renal injury	• Acute renal failure SMQ (Broad)
	• PTs:
	  ○ Blood urine
	  ○ Blood urine present
	  ○ Glomerulonephritis
	  ○ Hematuria
	  ○ Urine albumin/creatinine ratio abnormal
	  ○ Urine albumin/creatinine ratio increased
	  ○ Focal segmental glomerulosclerosis
		Nephropathy toxic is PT captured in this SMQ, LLT is drug-induced kidney injury

Thrombocytopenia	• Hematopoietic thrombocytopenia SMQ (broad) • Hemorrhage terms (excl laboratory terms) SMQ – this is a sub-SMQ of hemorrhages SMQ	Hematopoietic thrombocytopenia is a sub-SMQ of hematopoietic cytopenias SMQ Hemorrhage terms (excl laboratory terms) SMQ is a sub-SMQ of hemorrhages SMQ
Injection site reactions	• PTs: o Injection site urticaria o Injection site thrombosis o Injection site extravasation o Injection site erosion o Injection site erythema o Injection site granuloma o 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 ○ Injection site panniculitis ○ Injection site phlebitis ○ Injection site pruritic ○ Injection site abscess ○ Injection site anesthesia ○ Injection site cellulitis ○ Injection site discoloration ○ Injection site discomfort ○ Injection site warmth	

Neutropenia*	• PTs: ○ Neutropenia ○ Granulocytopenia ○ Neutrophil count decreased ○ Neutrophil count abnormal ○ Neutrophil percentage decreased ○ Leukopenia	

MedDRA V28.1.

Adverse events of special interest (AESI) are subsets of events reported as AEs. AESI for bepirovirsen were defined based on non-clinical data and clinical effects observed with other 2'MOE ASOs and based on data emerging from the clinical program. AESI categories are set up prior to the read-out of the clinical studies and are comprised of Standardised MedDRA Queries (SMQs) where available and selected MedDRA preferred terms. SMQs are a validated grouping of MedDRA terms designed to identify and analyze specific safety topics in a consistent manner. Hence, the AESIs categories count all AEs from the trials that are coded with any of the MedDRA-defined preferred terms from SMQs or selected preferred terms. However, the SMQs often encompass a broad range of terms that may extend beyond the specific safety question for the B-Well clinical study. The AESI list does not influence how investigators reported events; it is used to support structured review and analysis of safety data.

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*Closely monitored events, not classified as AESI.

AESI, adverse event of special interest; ALT, alanine aminotransferase; 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.