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Phase 3 Results of Bepirovirsen Treatment for Chronic Hepatitis B Virus Infection

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ABSTRACT

BACKGROUND

Treatment with bepirovirsen, an antisense oligonucleotide targeting hepatitis B virus (HBV) transcripts, has the potential to result in a functional cure, defined by at least 24 weeks of a sustained HBV DNA level below the lower limit of quantification (LLOQ) and hepatitis B surface antigen (HBsAg) loss after fixed-duration therapy.

METHODS

In two replicate, double-blind trials (B-Well 1 and B-Well 2), we randomly assigned adults with noncirrhotic chronic HBV infection in a 2:1 ratio to receive subcutaneous bepirovirsen (at a weekly dose of 300 mg) or placebo for 24 weeks. All the patients were receiving stable nucleoside or nucleotide analogue (NA) therapy and had an HBsAg level of more than 100 to 3000 IU per milliliter. Eligible patients discontinued NA therapy at 48 weeks. The primary outcome was a functional cure at week 72.

RESULTS

The percentage of patients with a functional cure at week 72 was significantly higher with bepirovirsen than with placebo both in the B-Well 1 trial (in 127 of 650 patients [20%] vs. none of 328 patients) and in the B-Well 2 trial (in 106 of 570 patients [19%] vs. none of 286 patients). In a pooled analysis at 72 weeks, adverse events were reported in 91% of the patients in the bepirovirsen groups and in 73% of those in the placebo groups; serious adverse events were reported in 7% and 4% of the patients, respectively. During the treatment period, adverse events of grade 3 or higher were reported in 16% of the patients who received bepirovirsen and in 3% of those who received placebo; increases in the alanine aminotransferase level were the most common grade 3 adverse events with bepirovirsen (in 6% of the patients).

CONCLUSIONS

In two phase 3 trials involving patients with chronic HBV infection, a functional cure after the discontinuation of NA therapy was reported in significantly more patients treated with bepirovirsen than in those who received placebo. (Funded by GSK; ClinicalTrials.gov numbers, NCT05630807 and NCT05630820.)

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*A list of the members of the B-Well Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Chronic hepatitis B virus (HBV) infection is a serious global health issue affecting 240 million people worldwide and causing over a million deaths annually.[1] Persons with chronic HBV infection often have a reduced quality of life and face stigma and discrimination.[2,3]

A functional cure, defined as an HBV DNA level below the lower limit of quantification (LLOQ) and hepatitis B surface antigen (HBsAg) loss (i.e., a level of <0.05 IU per milliliter) for at least 24 weeks after finite (fixed-duration) therapy — with or without a positive test for hepatitis B surface antibody — is the treatment goal for patients with chronic HBV infection and the recommended end point for new finite HBV therapies.[4,5] HBsAg loss is associated with better clinical outcomes than HBV DNA suppression alone, but it is rarely achieved with currently approved therapies, which include nucleoside and nucleotide analogues (NAs) and pegylated interferon.[4-8] In addition to showing the benefits of HBsAg loss, a functional cure ends the need for further NA treatment, therefore removing the risk of virologic breakthrough from resistance or nonadherence, along with the costs and side effects of long-term NA therapy.[5,9-11]

Bepirovirsen is an unconjugated antisense oligonucleotide that targets all HBV transcripts, thereby reducing levels of HBV DNA and HBsAg.[12,13] In addition to its direct antiviral effects, bepirovirsen also stimulates the immune response, with evidence of cytokine induction and immune-cell activation.[14-16] Extended follow-up of the phase 2 bepirovirsen studies showed that some patients with a baseline HBsAg level of 3000 IU per milliliter or less who received a course of bepirovirsen were able to discontinue NA therapy and have a durable functional cure.[12,17,18]

Here, we present the key efficacy and safety results of the phase 3 B-Well 1 and B-Well 2 trials involving patients with NA-suppressed chronic HBV infection. In these trials, we assessed the percentage of patients who had a functional cure with 24 weeks of bepirovirsen therapy, as compared with placebo.

Methods

Trial Design and Oversight

From December 6, 2022, to May 16, 2024, patients were recruited in the double-blind, placebo-controlled B-Well 1 and B-Well 2 trials (identical in design), which were conducted in 29 countries across Europe, the Asia–Pacific region, and the Americas. The trial funder, GSK, designed and monitored the trial conduct, data collection, and analysis. The trial protocols (available with the full text of this article at NEJM.org) were approved by the relevant institutional review board or ethics committee at each site. All the patients provided written informed consent.

A hepatitis B patient council provided input into the trial design. An independent data and safety monitoring committee reviewed the unblinded data. An independent hepatic adjudication committee assessed serious adverse events and protocol-defined permanent treatment discontinuations associated with biochemical changes to the liver in order to adjudicate the most likely cause for the event.

A medical writer who was funded by GSK prepared the first draft of the manuscript under the direction of the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trials to the protocols.

Patients

We enrolled adults with documented chronic HBV infection who had been receiving stable NA therapy for at least 6 months before screening and had no planned regimen changes during the trial. All the patients had an HBsAg level ranging from 100 to 3000 IU per milliliter, an HBV DNA level of less than 90 IU per milliliter, and an alanine aminotransferase (ALT) level of no more than two times the upper limit of the normal range.

Key exclusion criteria were the receipt of interferon-containing therapy within 12 months before screening; a history of or suspected cirrhosis, as determined by protocol-specified criteria that were based on noninvasive biomarkers or historical record of cirrhosis from liver-stiffness measurement or biopsy or confirmed clinical diagnosis; coinfection with hepatitis C, human immunodeficiency virus, or hepatitis D; a history of vasculitis or associated disease or autoimmune condition; or a platelet count of less than 140,000 per cubic millimeter. Patients who had positive results on testing for hepatitis B e antigen (HBeAg) were initially excluded from enrollment until the adoption of a protocol amendment in March 2023. Full eligibility criteria are detailed in the protocols.

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RANDOMIZATION AND TREATMENT

The patients were randomly assigned in a 2:1 ratio to receive bepirovirsen or placebo through a central interactive response system, with stratification according to the screening HBsAg level (100 to 1000 IU per milliliter [lower HBsAg stratum] or 1000 to 3000 IU per milliliter [higher HBsAg stratum]) (Fig. 1). Bepirovirsen (at a dose of 300 mg) or placebo was administered through weeks 1 to 24 as weekly subcutaneous injections (two injections per administration), with a loading dose on days 4 and 11 (treatment period). All the patients were also receiving background NA therapy during this period. The patients continued to receive NA therapy through weeks 24 to 48 (NA-only stage); eligible patients discontinued NA therapy at week 48. Eligibility for NA discontinuation required a level of HBV DNA that was below the LLOQ (<20 IU per milliliter or not detected, as assessed with the COBAS assay [Roche]) and no detection of HBsAg (as assessed with the Elecsys HBsAg II assay [Roche], with a limit of detection of <0.05 IU per milliliter) from week 24 to week 46, as well as an ALT value of two times the upper limit of the normal range or less and negativity for HBeAg at week 46.

Treatment response was assessed at week 72, which was 24 weeks after the discontinuation of all HBV treatment in eligible patients. An ongoing assessment of the durability of response was scheduled to be performed up to week 96 (results not reported here). Additional information regarding the trial conduct and assay measures is provided in the Methods section of the Supplementary Appendix, available at NEJM.org.

OUTCOMES

The primary outcome was a functional cure at week 72, as assessed by an HBV DNA level below the LLOQ (<20 IU per milliliter or not detected), HBsAg not detected (qualitative assay, <0.05 IU per milliliter), and no receipt of rescue therapy. Three multiplicity-controlled key secondary efficacy outcomes were evaluated: a functional cure at week 72 among the patients in the lower HBsAg stratum, the discontinuation of NA ther-

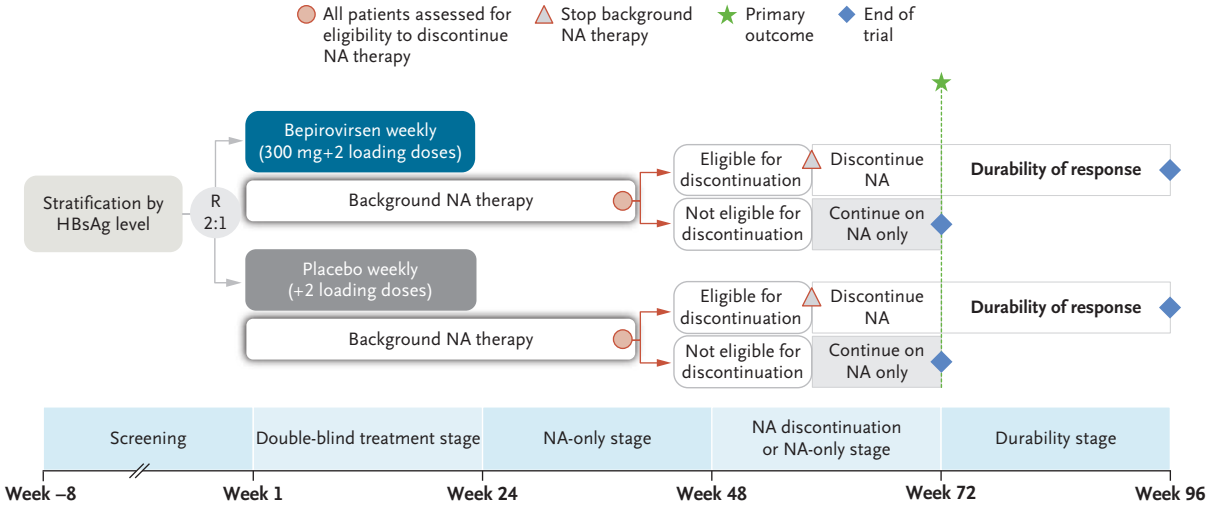


Figure 1. B-Well 1 and B-Well 2 Trial Design.

The B-Well 1 and 2 trials were designed to have an identical format for replication purposes, with the exception of an optional exit interview in B-Well 1 (not reported in this article). After a screening window of 45 days, randomization could extend to 60 days with a medical monitoring agreement (e.g., waiting for retesting results). Patients were stratified according to the hepatitis B surface antigen (HBsAg) level (>100 to ≤1000 IU per milliliter [lower HBsAg stratum] or >1000 to ≤3000 IU per milliliter [higher HBsAg stratum]). Trial treatments were two subcutaneous injections administered once weekly, except during weeks 1 and 2, which had additional loading doses on days 4 and 11. All the patients were receiving stable nucleoside or nucleotide analogue (NA) therapy at baseline. To be eligible for NA discontinuation at week 48, a hepatitis B virus (HBV) DNA level below the lower limit of quantification (LLOQ; <20 IU per milliliter or not detected) was required, along with HBsAg loss (qualitative assay, <0.05 IU per milliliter) from week 24 to week 46; an alanine aminotransferase value that was no more than two times the upper limit of the normal range at week 46; and negative results on testing for hepatitis B e antigen at week 46. The evaluation of findings obtained in the durability stage is ongoing.

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apy and maintenance of an HBV DNA level below the LLOQ at week 72, and the discontinuation of NA therapy and maintenance of an HBV DNA level below the LLOQ at week 72 among patients in the lower HBsAg stratum. Safety was assessed by an evaluation of adverse events and laboratory monitoring.

Exploratory subgroup analyses were conducted to assess the percentage of patients with a functional cure across subgroups that were predefined according to such variables as the baseline HBsAg level and HBeAg status. Additional exploratory outcomes — including levels of HBsAg and ALT over time, HBeAg loss, and seroconversion to hepatitis B surface antibody — are reported.

STATISTICAL ANALYSIS

We determined that the enrollment of at least 750 patients in each of the B-Well trials would provide the trial with more than 99% power to determine the primary outcome with a two-sided alpha level of 0.05. A combined sample size of approximately 1800 patients in the two trials would provide adequate safety data. All the patients who had undergone randomization and received at least one dose of bepirovirsen or placebo were included in the efficacy and safety analyses.

In each trial, a fixed sequence of hierarchical testing was prespecified and performed for the primary and key secondary efficacy outcomes to preserve the overall probability of a type I error at a two-sided significance level of 0.05. Patients with missing data that precluded the efficacy assessment were classified as having a nonresponse.

We calculated the common risk difference using the summary Miettinen–Nurminen method across the two baseline HBsAg strata (≤1000 IU and >1000 IU per milliliter) along with a two-sided 95% confidence interval. We used the same baseline strata to assess the treatment effect for patients who had a baseline HBsAg value of 3000 IU per milliliter or less (primary outcome and key secondary outcome). The treatment effect for key secondary outcomes among the patients in the lower HBsAg stratum was assessed according to the between-group difference in the percentage of patients with a response and the calculation of a two-sided 95% confidence interval.

The efficacy assessments at week 72 permitted blips, which were defined as a single result of a detectable HBsAg or HBV DNA level that was equal to or greater than the LLOQ and that was both preceded and immediately followed by an HBsAg level that was not detected or an HBV DNA level that was below the LLOQ. Additional details regarding the statistical analysis are provided in the Supplementary Appendix. Descriptive analyses of the primary and key secondary efficacy outcomes were conducted with pooled data from both trials. The widths of the 95% confidence intervals have not been adjusted for multiple testing and should not be used in place of hypothesis testing. Safety data were summarized descriptively and are presented for each trial and pooled across the two trials.

RESULTS

PATIENTS

In the B-Well 1 and 2 trials, 1838 patients underwent randomization: 1224 to receive bepirovirsen (653 patients in B-Well 1 and 571 patients in B-Well 2) and 614 to receive placebo (328 patients in B-Well 1 and 286 in B-Well 2) (Fig. S1 in the Supplementary Appendix). No bepirovirsen or placebo was administered to 4 randomly assigned patients (3 in B-Well 1 and 1 in B-Well 2), so these patients were excluded from the full analysis population (leaving 1834 patients). Three patients who were assigned to the placebo group (2 in B-Well 1 and 1 in B-Well 2) received bepirovirsen in error and were therefore included in the bepirovirsen safety population (1223 patients); the placebo safety population included 611 patients. Treatment completion was similar across the two trials and trial groups (89 to 93%).

The baseline characteristics of the patients were similar in the groups across the two trials (Table 1). The mean (±SD) HBsAg level ranged from 914±760 IU per milliliter to 955±741 IU per milliliter across the trial groups, and 63% of the patients had a baseline HBsAg level of 1000 IU per milliliter or less. The demographic characteristics were generally representative of patients affected by chronic HBV infection in clinical practice (Table S1).

NA DISCONTINUATION AT WEEK 48

At week 48, NA therapy was discontinued in the bepirovirsen group in 159 of 650 patients (24%) in B-Well 1 and in 136 of 570 patients (24%) in B-Well 2 on the basis of results of laboratory testing; no patients in the placebo group discontinued NA therapy (Table S2). Among the patients

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	B-Well 1		B-Well 2	
	Bepirovirsen (N=653)	Placebo (N=328)	Bepirovirsen (N=571)	Placebo (N=286)
Age — yr	50.2±11.8	49.2±10.6	48.7±10.4	49.2±11.4
Male sex — no. (%)	461 (71)	227 (69)	414 (73)	202 (71)
Race or ethnic group — no. (%)†				
Asian	440 (67)	229 (70)	388 (68)	195 (68)
White	168 (26)	78 (24)	149 (26)	78 (27)
Black	31 (5)	18 (5)	25 (4)	11 (4)
Multiple	7 (1)	2 (1)	1 (<1)	2 (1)
American or Alaskan First Nations	7 (1)	1 (<1)	1 (<1)	0
Native Hawaiian or other Pacific Islander	0	0	7 (1)	0
Hispanic or Latino ethnic group — no. (%)†				
Yes	81 (12)	25 (8)	27 (5)	20 (7)
No	561 (86)	296 (90)	542 (95)	264 (92)
Not reported or unknown	11 (2)	7 (2)	2 (<1)	2 (1)
Hepatitis B surface antigen‡				
Mean — IU/ml	952±1047	914±760	955±741	919±691
Distribution — no. (%)				
≤1000 IU/ml	427 (65)	214 (65)	343 (60)	179 (63)
>1000 to ≤3000 IU/ml	226 (35)	114 (35)	228 (40)	107 (37)
Log_{10} — IU/ml	2.80±0.41	2.79±0.45	2.83±0.39	2.82±0.37
Hepatitis B virus DNA <20 IU/ml — no. (%)§	641 (98)	322 (98)	564 (99)	283 (99)
Hepatitis B e antigen–negative status — no. (%)	598 (92)	300 (91)	528 (92)	260 (91)
Alanine aminotransferase				
Mean — IU/liter	22.1±11.4	23.1±11.6	21.9±10.5	22.9±12.1
≤ULN — no. (%)	599 (92)	296 (90)	535 (94)	263 (92)
Current NA — no. (%)‡¶				
Entecavir	261 (40)	139 (42)	252 (44)	117 (41)
TAF, TDF, tenofovir, or TMF‖	395 (60)	189 (58)	324 (57)	169 (59)
Other NAs**	13 (2)	2 (1)	6 (1)	5 (2)

* Plus–minus values are means ±SD. ULN denotes upper limit of the normal range.
† Race and ethnic group were reported by the patients, with multiple selections permitted.
‡ The listed values are for 570 patients in the bepirovirsen group in B-Well 2.
§ The listed values are for 652 patients in the bepirovirsen group in B-Well 1.
¶ For current nucleoside or nucleotide analogue (NA) therapy at baseline, the categories are not mutually exclusive; a patient may have been counted in more than one category.
‖ TAF includes tenofovir alafenamide and tenofovir alafenamide fumarate; TDF includes tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil orotate, and tenofovir disoproxil succinate; TMF includes tenofovir amibufenamide and tenofovir amibufenamide fumarate; and tenofovir includes tenofovir disoproxil maleate.
** Other NAs include emtricitabine, lamivudine, adefovir, besifovir dipivoxil maleate, alafenamide emtricitabine plus tenofovir, emtricitabine plus tenofovir disoproxil fumarate, and telbivudine.

in the bepirovirsen group in the lower baseline HBsAg stratum, NA therapy was discontinued in 131 of 426 patients (31%) in B-Well 1 and in 114 of 342 patients (33%) in B-Well 2.

FUNCTIONAL CURE AT WEEK 72

The percentage of patients with a functional cure at week 72 (the primary outcome) was significantly higher with bepirovirsen than with placebo,

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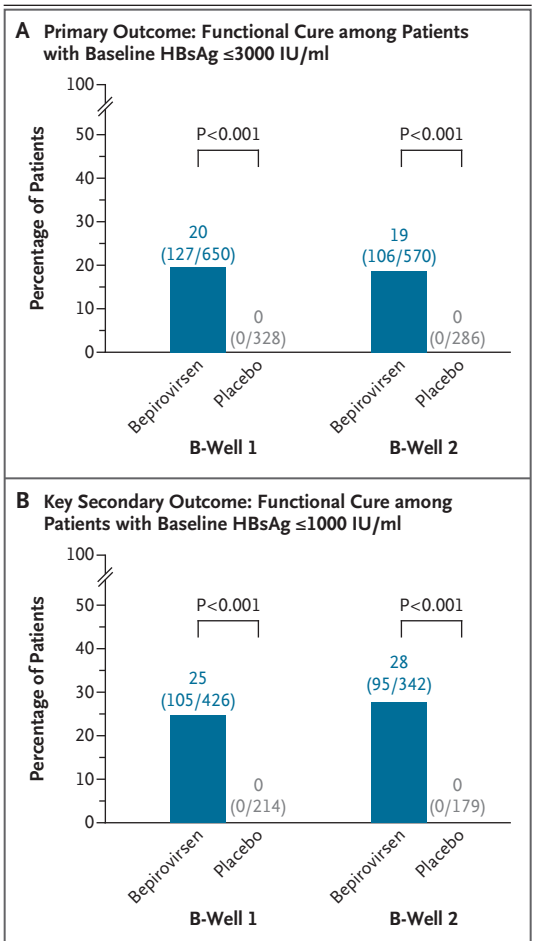


Figure 2. Functional Cure at Week 72 and Key Secondary Outcome, According to Baseline HBsAg Level.

Panel A shows the percentage of patients who had a functional cure (the primary outcome), which was defined as 24 weeks or more of a sustained HBV DNA level below the LLOQ (<20 IU per milliliter or not detected) and HBsAg loss (qualitative assay, <0.05 IU per milliliter). The common risk difference between the groups (calculated with the Miettinen–Nurminen method) was 17.5 percentage points (95% CI, 14.6 to 20.3) in the B-Well 1 trial and 13.3 percentage points (95% CI, 10.4 to 16.1) in the B-Well 2 trial. Panel B shows the percentage of patients who had a functional cure in those with a baseline HBsAg value of 1000 IU per milliliter or less (lower HBsAg stratum) — a key secondary outcome — for a difference of 24.6 percentage points (95% CI, 20.8 to 29.0) in B-Well 1 and 27.8 percentage points (95% CI, 23.3 to 32.8) in B-Well 2.

both in B-Well 1 (in 127 of 650 patients [20%] vs. none of 328 patients) and in the B-Well 2 trial (in 106 of 570 patients [19%] vs. none of 286 patients). The common risk difference (calculated with the Miettinen–Nurminen method) was 17.5 percentage points (95% confidence interval [CI], 14.6 to 20.3) in B-Well 1 and 13.3 percentage points (95% CI, 10.4 to 16.1) in B-Well 2 (P<0.001 for both comparisons) (Fig. 2A). The calculation of the common risk difference had greater weighting on the higher HBsAg stratum (i.e., a value of >1000 IU per milliliter at baseline) than on the lower HBsAg stratum (i.e., a value of ≤1000 IU per milliliter at baseline) because a lower percentage of patients in the higher stratum had a functional cure (Table S3). The treatment effect appeared to be generally consistent across subgroups (Fig. S2).

For the first of the three key secondary outcomes, among the patients in the lower HBsAg stratum, the percentage of patients with a functional cure was 25% with bepirovirsen and 0% with placebo in B-Well 1 (risk difference, 24.6 percentage points; 95% CI, 20.8 to 29.0; P<0.001) and 28% with bepirovirsen and 0% with placebo in B-Well 2 (risk difference, 27.8 percentage points; 95% CI, 23.3 to 32.8; P<0.001) (Fig. 2B). In the higher HBsAg stratum, the percentage of patients with a functional cure was 10% with bepirovirsen and 0% with placebo in B-Well 1 (risk difference, 9.8 percentage points; 95% CI, 6.4 to 14.4) and 5% with bepirovirsen and 0% with placebo in B-Well 2 (risk difference, 4.8 percentage points; 95% CI, 1.3 to 8.4). Descriptive analyses of the primary and key secondary efficacy outcomes with pooled data from B-Well 1 and B-Well 2 are shown in Figure S3. Among the patients who discontinued NA therapy, missing data prevented the assessment of a functional cure in five patients in B-Well 1 (four in the lower HBsAg stratum and one in the higher HBsAg stratum) and in no patients in B-Well 2. These cases of missing data in the bepirovirsen group were imputed as a nonresponse at week 72.

In general, the HBsAg value was less than 0.05 IU per milliliter by week 12 among the patients who had a functional cure (Fig. S4). Patients in the placebo group did not have notable changes in the mean HBsAg level during treatment.

HBV DNA AFTER NA DISCONTINUATION

The second key secondary outcome, a sustained HBV DNA level below LLOQ at week 72 after the discontinuation of NA therapy at week 48, was reported in 151 of 650 patients (23%) in the bepirovirsen group and in 0% in the placebo group (P<0.001) in B-Well 1 (Fig. 3A). This outcome was reported in 132 of 570 patients (23%)

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in the bepirovirsen group and in 0% in the placebo group (P<0.001) in B-Well 2. A sustained HBV DNA level below the LLOQ after NA discontinuation without a functional cure (i.e., without an HBsAg level of <0.05 IU per milliliter) was observed in 24 of 650 patients (4%) in the bepirovirsen group in B-Well 1 and in 26 of 570 patients (5%) in B-Well 2 (Table S4). After discontinuing NA therapy, 5 of 295 patients (2%) who received bepirovirsen had HBV DNA replication (<2000 IU per milliliter) at week 72; however, none had virologic or clinical relapse (Table S2).

The third key secondary outcome, a sustained HBV DNA value below the LLOQ after the discontinuation of NA therapy among patients in the lower HBsAg stratum, was reported in 124 of 426 patients (29%) in B-Well 1 and in 113 of 342 patients (33%) in B-Well 2 (P<0.001) (Fig. 3B). In the higher HBsAg stratum, a sustained HBV DNA value below the LLOQ after the discontinuation of NA therapy was reported in 27 of 224 patients (12%) in B-Well 1 and in 19 of 228 patients (8%) in B-Well 2. Descriptive analyses of the key secondary efficacy outcomes with pooled data from B-Well 1 and B-Well 2 are shown in Figure S3.

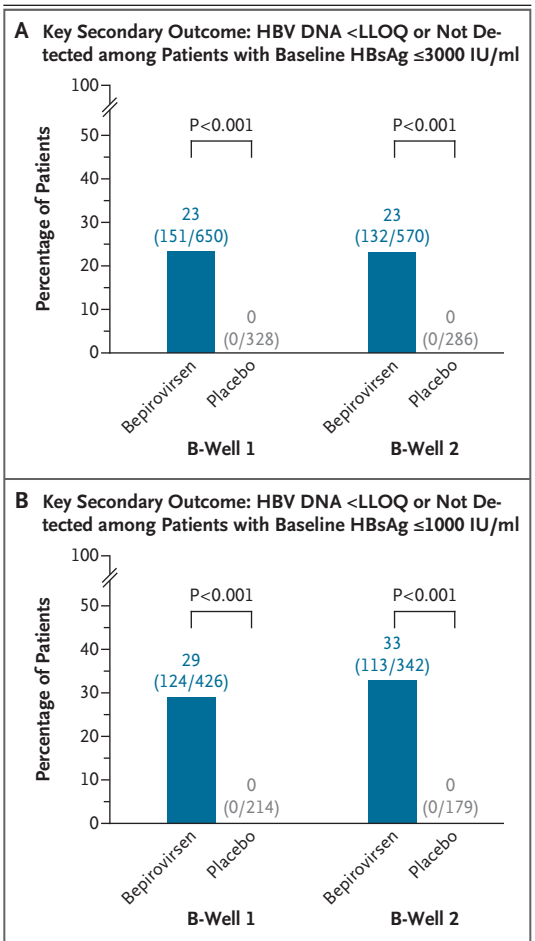


Figure 3. Discontinuation of NA and HBV DNA below LLOQ or Not Detected at Week 72, According to Baseline HBsAg Level.

Shown is the percentage of patients who had an HBV DNA value that was below the LLOQ (<20 IU per milliliter or not detected) at week 72, according to whether they had a baseline HBsAg level of 3000 IU per milliliter or less (Panel A) or a baseline level of 1000 IU per milliliter or less (Panel B) (two key secondary outcomes). In Panel A, the common risk difference was 21.0 percentage points (95% CI, 17.9 to 24.0) in B-Well 1 and 18.2 percentage points (95% CI, 15.1 to 21.3) in B-Well 2. In Panel B, the risk difference was 29.1 percentage points (95% CI, 25.0 to 33.6) in B-Well 1 and 33.0 percentage points (95% CI, 28.3 to 38.2) in B-Well 2.

CHANGES IN HBSAG AND ALT OVER TIME

Increases in the ALT level of at least three times the upper limit of the normal range were observed in 24% of the patients in the bepirovirsen groups in weeks 1 to 24 (Table S5). ALT increases occurred primarily during weeks 5 to 10 in parallel with decreases in HBsAg values (Fig. S5). The ALT increases were usually associated with a reduction in the HBsAg level of more than 3 $\log_{10}$ IU per milliliter (Fig. S6).

HBEAG AND ANTI-HBE

In both B-Well 1 and B-Well 2, a total of 8% of patients had a positive test for HBeAg at baseline (Table 1). Among those who received bepirovirsen, HBeAg loss had occurred by week 72 in 16 of 55 patients (29%) in B-Well 1 and in 11 of 43 patients (26%) in B-Well 2. Of these patients, hepatitis B e antibody (anti-HBe) developed in 3 of 55 patients (5%) in B-Well 1 and in 3 of 43 patients (7%) in B-Well 2. Among the patients who received placebo, HBeAg loss occurred in 3 of 28 patients (11%) in B-Well 1 and in 2 of 26 patients (8%) in B-Well 2, along with the development of anti-HBe in 1 of 28 patients (4%) and in no patients, respectively (Table S6). Among the HBeAg-positive patients at baseline, HBeAg loss and a functional cure occurred in 6 of 55 patients (11%) in B-Well 1 and in 2 of 43 patients (5%) in B-Well 2.

HEPATITIS B SURFACE ANTIBODY

Among the patients with a negative baseline value for hepatitis B surface antibody (<10 IU per liter)

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Table 2. Safety Summary during Weeks 1 to 24 (Treatment Period).*

Event	B-Well 1		B-Well 2		Pooled Data	
	Bepirovirsen (N=652)	Placebo (N=326)	Bepirovirsen (N=571)	Placebo (N=285)	Bepirovirsen (N=1223)	Placebo (N=611)
	number of patients (percent)					
Any adverse event	575 (88)	210 (64)	512 (90)	189 (66)	1,087 (89)	399 (65)
Leading to permanent dose discontinuation	26 (4)	0	15 (3)	2 (<1)	41 (3)	2 (<1)
Leading to dose reduction	13 (2)	0	11 (2)	0	24 (2)	0
Leading to dose interruption or delay	100 (15)	10 (3)	93 (16)	3 (1)	193 (16)	13 (2)
Adverse event of grade ≥3 severity†	96 (15)	8 (2)	101 (18)	8 (3)	197 (16)	16 (3)
Adverse event related to bepirovirsen or placebo‡	512 (79)	111 (34)	469 (82)	104 (36)	981 (80)	215 (35)
Any serious adverse event	25 (4)	5 (2)	23 (4)	3 (1)	48 (4)	8 (1)
Related to bepirovirsen or placebo‡	12 (2)	0	11 (2)	0	23 (2)	0
Fatal§	0	0	1 (<1)	0	1 (<1)	0

* All the patients in the two trials received bepirovirsen or placebo through weeks 1 to 24 (treatment period) as two subcutaneous injections administered once weekly. Categories of adverse events were not mutually exclusive, so patients may have been counted in more than one category.

† Adverse events 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 an event resulting in death. The investigator's judgment may have been used in assigning clinical severity and may not always align with DAIDS grading.

‡ The determination of whether an adverse event was related to the receipt of bepirovirsen or placebo was made by the trial investigator.

§ None of the fatal events were considered by the investigator to be related to the receipt of bepirovirsen. In the B-Well 2 trial during the treatment period, a death from aortic dissection occurred at 25 days after the initiation of bepirovirsen, with autopsy findings indicative of cardiovascular disease. In the B-Well 1 trial, a death in the bepirovirsen group occurred after a reported "near drowning" during weeks 37 to 48, 10 months after the last administration of bepirovirsen. In the bepirovirsen group, a patient died from pancreatic cancer after withdrawal from the trial.

who had a functional cure, post hoc analysis showed that a hepatitis B surface antibody level of 10 IU or more per liter developed in 79 of 118 patients (67%) in B-Well 1 and in 66 of 103 patients (64%) in B-Well 2. The mean levels of hepatitis B surface antibody varied among the patients in the bepirovirsen groups, with no notable changes in the placebo groups (Table S7).

SAFETY

The safety profile of bepirovirsen was consistent across B-Well 1 and B-Well 2. Therefore, analyses of pooled safety results are reported. By week 72, adverse events were reported in 91% of the patients in the bepirovirsen groups and in 73% of those in the placebo groups; severe adverse events were reported in 7% and 4% of the patients, respectively (Table S8).

From week 1 to week 24 (treatment period), adverse events were reported in 89% of the patients in the bepirovirsen groups and in 65% of those in the placebo groups (Table 2); most of these events were reported by week 12. Most adverse events with bepirovirsen during the treatment period were those captured as being of special interest (Table 3 and Table S9). Of these events, injection-site reactions were the most common (in 53% of the patients in the bepirovirsen groups and in 14% of those in the placebo groups); these reactions occurred most commonly during the first 4 weeks of treatment. The majority of such events were mild, and none were classed as serious. Serious adverse events during the treatment period were infrequent in both the bepirovirsen groups and the placebo groups (4% vs. 1%). Serious adverse events that were considered by the investigator to be related to bepirovirsen occurred in 2% of the patients (Table 2 and Table S10).

Adverse events of grade 3 or higher were reported in 16% of the patients in the bepirovirsen groups and in 3% of those in the placebo groups during the treatment period (weeks 1 to 24) (Table 2). The most common of these events (in the bepirovirsen groups only) was an increase in the ALT level (in 6% of the patients). Adverse events that led to permanent treatment discon-

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Table 3. Selected Adverse Events of Special Interest and Key Laboratory Abnormalities during Weeks 1 to 24 and Weeks 25 to 48 (Pooled Safety Population).*

Event or Abnormality	Pooled Data from B-Well 1 and B-Well 2			
	Weeks 1 to 24		Weeks 25 to 48	
	Bepirovirsen	Placebo	Bepirovirsen	Placebo
	number of patients/total number (percent)			
Injection-site reaction	648/1223 (53)	84/611 (14)	45/1173 (4)	1/566 (<1)
Laboratory abnormality				
Hepatobiliary: alanine aminotransferase level ≥3× ULN	292/1221 (24)	2/609 (<1)	11/1170 (1)	1/564 (<1)
Hematologic: platelet count of <100,000 per mm^3	100/1223 (8)	3/611 (<1)	53/1223 (4)	1/611 (<1)
Renal				
Change from baseline of >0.5 mg/dl in serum creatinine level†	31/1223 (3)	9/611 (1)	11/1223 (1)	4/611 (1)
Urinary albumin:creatinine ratio of >300‡	18/1223 (1)	7/611 (1)	13/1223 (1)	6/611 (1)

* Injection-site reaction was a selected adverse event of special interest. All other events listed are key laboratory abnormalities that occurred during the specified time frames.
† To convert the values for creatinine to micromoles per liter, multiply by 88.4.
‡ In this ratio, albumin was measured in milligrams and creatinine in grams.

tinuation occurred in 3% of the patients in the bepirovirsen groups. During the treatment period, adverse events of special interest in the category of vascular inflammation, complement activation, and other immune-associated effects were reported in 33% of the patients in the bepirovirsen groups and in 12% of those in the placebo groups; less than 1% of patients met the criteria for pausing or stopping treatment for potential drug-induced vascular injury and complement events. Potential events of drug-induced vascular injury generally manifested as cutaneous vasculitis, with skin purpuric rash with or without joint pain; such events resolved after treatment discontinuation. All adverse events that met the protocol-defined criteria for pausing or stopping treatment are reported in Table S11. Two deaths that were assessed as being unrelated to treatment were reported in the bepirovirsen groups (Table 2). In the bepirovirsen group, a patient died from pancreatic cancer after withdrawing from the trial. This serious adverse event was assessed by the investigator as not related to treatment.

Selected hematologic, hepatobiliary, and renal abnormalities are reported (Table 3 and Table S5). No patients met the criteria for drug-induced liver injury. Decreases in mean values for both the platelet count and the estimated glomerular filtration rate (eGFR) were observed during bepirovirsen treatment, with levels returning to near baseline by week 72 (Figs. S7 and S8A). The percentage of patients who had an eGFR of less than 90 ml per minute per 1.73 m^2 of body-surface area increased during bepirovirsen treatment (Fig. S8B). By week 48, the distribution of patients across relative eGFR categories was not substantially different from that in the placebo group and resembled the distribution at week 2. Two patients in the bepirovirsen group had a platelet count of less than 50,000 per cubic millimeter at one visit, which met the criterion for permanent discontinuation. A platelet count of less than 100,000 per cubic millimeter at any visit was observed in 119 of 1223 patients (10%) in the bepirovirsen groups and in 3 of 611 patients (<1%) in the placebo groups. No clinically meaningful bleeding events attributed to bepirovirsen were reported.

DISCUSSION

In these two multicountry phase 3 trials involving patients with virologically suppressed chronic HBV infection during receipt of NA therapy, significantly more patients who were assigned to receive 24 weeks of bepirovirsen and then stopped all anti-HBV treatment had a functional cure than those who were assigned to receive placebo (20% in B-Well 1 and 19% in B-Well 2, as com-

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pared with no patients in the placebo group). Among the patients in the lower HBsAg stratum (≤1000 IU per milliliter at baseline), the percentage of patients who had a functional cure with bepirovirsen was 25% in B-Well 1 and 28% in B-Well 2; the percentages were 10% and 5%, respectively, in the higher HBsAg stratum (>1000 IU per milliliter).

Regulatory body guidance for clinical trials of HBV therapies and the Treatment End Points Conference of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) support the primary outcome of functional cure for finite HBV therapies.[4,19,20] In addition to functional cure, a sustained HBV DNA level below the LLOQ is an alternative outcome endorsed by regulatory bodies for finite therapies.[19,20] The HBV DNA target was met at week 72 in 23% of the patients receiving bepirovirsen in B-Well 1 and in 23% of those in B-Well 2; among the patients in the lower HBsAg stratum, that target was met in 29% and 33% of the patients in the two trials, respectively. Among the limited number of HBeAg-positive patients (8% of all enrollees), a functional cure by week 72 occurred in 11% and 5% of bepirovirsen-treated patients, respectively.

The replicate trial design and multicountry enrollment across B-Well 1 and B-Well 2 provide robust evidence for the efficacy and safety of bepirovirsen in patients with chronic HBV infection worldwide. Assessment of the durability of the off-treatment response in the B-Well trials is ongoing and will be further evaluated in the B-Sure trial.[21]

Limitations of the phase 3 trials include the relatively small numbers of patients who were included in subgroup analyses and the small numbers in certain racial and ethnic groups (e.g., Black and Hispanic or Latino patients), which may limit generalizability for some groups of patients. Another limitation is central stratification during randomization, which may have resulted in differing average baseline HBsAg levels in different countries, although the treatment effect across subgroups appeared to be generally consistent. Population-level data regarding quantitative HBsAg levels are limited; however, available cohort and registry analyses (including data for patients regardless of treatment received and HBeAg status) suggest that approximately two thirds of patients with available data regarding quantitative HBsAg values may meet the criterion of an HBsAg value of 3000 IU per milliliter or less for eligibility that was used in the B-Well trials.[22-24] However, these estimates vary across clinical and geographic settings and are influenced by patient selection (including age, treatment status, and disease phase) and testing practices. Broader implementation of quantitative HBsAg testing will be essential for identifying eligible patients in clinical practice.

Sequential or combination strategies with complementary HBV therapies may increase the percentage of patients who can have a functional cure with bepirovirsen. Several potentially complementary methods are under investigation, including the inhibition of noncanonical poly(A) RNA polymerase-associated domains containing proteins 5 and 7 (PAPD5 and PAPD7),[25] a small interfering RNA (as described in the B-United study[26]), and HBV-targeted immunotherapy.[27] The investigation of the use of pegylated interferon after bepirovirsen treatment in the B-Together study[28] suggested that this drug may contribute to the durability of HBsAg loss and HBV DNA suppression off-treatment in some patients.

The higher incidence of adverse events with bepirovirsen than with placebo was mostly linked to the known class effects of bepirovirsen and other antisense oligonucleotides.[29] Decreases in the platelet count and eGFR resolved after treatment was completed or paused. Clinically meaningful reductions in eGFR were not associated with other markers of renal injury. In most cases, ALT increases did not require treatment modification. Transient ALT increases after bepirovirsen initiation were associated with a reduction in HBsAg levels and are recognized as markers of a therapeutic response to bepirovirsen.[12,14,15] Regular monitoring for laboratory abnormalities and temporarily pausing bepirovirsen administration were effective strategies to mitigate the development of clinically meaningful adverse events, and few events resulted in permanent discontinuation. The adoption of recommended monitoring and dose-modification criteria in clinical practice will be paramount to supporting the patient in receiving optimal benefit of treatment and ensuring that the development of serious clinical consequences is kept to a minimum.

In two phase 3 trials, 24 weeks of bepirovirsen therapy induced a functional cure in 20% and 19% of patients with virologically suppressed chronic HBV infection and a baseline HBsAg value of 3000 IU per milliliter or less. These findings support the efficacy of bepirovirsen as a 24-week fi-

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nite therapy to achieve functional cure and show added benefit over continued NA therapy as standard care in these patients.

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