

Elebsiran and PEG-IFN α for chronic hepatitis B infection: a partially randomized, open-label, phase 2 trial

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Functional cure is a goal for the treatment of chronic hepatitis B virus (HBV) infection; however, it is infrequently achieved with currently approved treatments. Here we provide a randomized evaluation of the small interfering RNA elebsiran, in combination with pegylated interferon alfa (PEG-IFN α), compared with PEG-IFN α monotherapy. In addition, this study evaluates the potential role of the HBV therapeutic vaccine BRII-179 in identifying immunologically responsive patients and improving hepatitis B surface antigen (HBsAg) loss rates. In part I (cohorts 1–3), virally suppressed participants with chronic HBV infection naive to BRII-179 were randomized 1:1:1 to receive 48 weekly doses of PEG-IFN α alone or in combination with 13 doses of elebsiran (200 mg or 100 mg) administered every 4 weeks. In part II (cohort 4), participants who had previously received 9 doses of elebsiran and BRII-179 in a prospective study (BRII-179-835-001) were categorized as BRII-179 anti-HBs responders or nonresponders based on their peak hepatitis B surface antibody (anti-HBs) levels (≥ 10 IU l $^{-1}$ or < 10 IU l $^{-1}$, respectively) and subsequently received 13 doses of elebsiran 100 mg every 4 weeks plus 48 weekly doses of PEG-IFN α . Primary endpoints were HBsAg loss at the end of treatment (EOT) and 24 weeks post-EOT. In part I, at 24 weeks post-EOT, HBsAg loss was observed in 4 out of 19 (21.1%) participants receiving elebsiran 200 mg plus PEG-IFN α , 6 out of 18 (33.3%) participants receiving elebsiran 100 mg plus PEG-IFN α and 1 out of 18 (5.6%) participants receiving PEG-IFN α monotherapy. In part II, HBsAg loss was observed in 9 out of 31 (29.0%) participants at 24 weeks post-EOT, with a higher response among BRII-179 anti-HBs responders (8 out of 19 participants, 42.1%) compared with nonresponders (1 out of 12 participants, 8.3%). Elebsiran and PEG-IFN α combination therapy was generally safe and well tolerated. These results demonstrate an additive benefit of elebsiran when combined with PEG-IFN α in achieving sustained HBsAg loss. Furthermore, the increased HBsAg loss rate in BRII-179 anti-HBs responders suggests that BRII-179 may be a valuable tool for immunological profiling to optimize curative outcomes in patients with HBV infection. ClinicalTrials.gov registration: [NCT05970289](https://clinicaltrials.gov/ct2/show/study/NCT05970289).

Chronic hepatitis B virus (HBV) infection remains a major global public health challenge, causing over 1.1 million deaths in 2022 from complications such as cirrhosis and liver cancer¹. An estimated 254 million people live with chronic HBV, with 1.2 million new infections annually². Functional cure, defined as sustained hepatitis B surface antigen (HBsAg) loss with or without hepatitis B surface antibody (anti-HBs) seroconversion and undetectable HBV DNA for at least 24 weeks off therapy³, is linked to better clinical outcomes and reduced relapse risk, which also helps to alleviate the social stigma of chronic HBV infection^{4–7}, thereby, making it a key treatment goal.

Approved treatment options for chronic HBV are limited. Long-term nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy, such as tenofovir or entecavir⁸, effectively suppresses viral replication but rarely achieves HBsAg loss^{9,10}, necessitating lifelong treatment. PEG-IFN α offers a finite-duration treatment with modest functional cure (<10%)^{11,12}, especially in patients with very low baseline HBsAg¹². However, its use is limited by notable adverse events and tolerability challenges. These limitations highlight the urgent need for effective, short-duration therapies. A multifaceted therapeutic approach, combining viral suppression and immune restoration or enhancement, may be essential to overcome HBV-induced immune dysfunction and achieve functional cure.

Elebsiran (BRII-835/VIR-2218) is a triantennary *N*-acetyl galactosamine (GalNAc)-conjugated small interfering RNA (siRNA) that is being developed for the treatment of chronic HBV infection and chronic hepatitis D virus infection. It targets a region of the *HBx* gene that is common to all HBV transcripts and is highly conserved across all HBV genotypes. In clinical studies, elebsiran monotherapy demonstrated reductions in serum HBsAg levels¹³. A prior study evaluating elebsiran in combination with PEG-IFN α reported an HBsAg loss rate of approximately 30% at the end of treatment (EOT) in participants with chronic HBV infection¹⁴. This rate was notably higher than historical HBsAg loss rates observed with PEG-IFN α monotherapy^{11,12}. However, this study lacked a PEG-IFN α monotherapy control, limiting direct comparison. In another study, BRII-179-835-001, elebsiran was investigated with or without BRII-179, a therapeutic vaccine composed of PreS1, PreS2 and SHBV surface antigens. The combination was shown to overcome HBV-induced immune dysfunction in a proportion of participants, as indicated by robust anti-HBs responses and PreS1/PreS2-specific CD4⁺ helper T cell responses¹⁵. As expected, no anti-HBs and/or PreS1/PreS2 responses were observed in the elebsiran alone cohort. It was hypothesized that individuals with chronic HBV infection who were able to overcome HBV-induced immune dysfunction following exposure to BRII-179 may have an increased likelihood of mounting an effective immune response upon subsequent treatment with elebsiran and PEG-IFN α , potentially leading to higher rates of functional cure.

Therefore, we conducted an open-label, phase 2 study (ENSURE, NCT05970289) consisting of two parts (Extended Data Fig. 1). Part I was a randomized study (cohorts 1–3) evaluating the efficacy and safety of elebsiran in combination with PEG-IFN α compared with PEG-IFN α monotherapy in virally suppressed participants with chronic HBV infection. Part II was a single-arm study (cohort 4) assessing the efficacy of elebsiran plus PEG-IFN α in participants who had previously completed nine doses of elebsiran and BRII-179 treatment in the BRII-179-835-001 study¹⁵. These participants were grouped into BRII-179 anti-HBs responders and nonresponders on the basis of their peak anti-HBs titers (≥ 10 IU l⁻¹ and <10 IU l⁻¹, respectively) by week 44 in the previous study. Here, we report ENSURE study results through 24 weeks post-EOT across cohorts 1–4. The study is still ongoing, with all remaining participants currently being monitored during the NRTI discontinuation monitoring period (Methods).

Results

Study participant disposition and baseline characteristics

From 9 August 2023 to 5 December 2023, 73 participants were screened in part I. Recruitment was paused when the minimal enrollment target

was met, and a total of 55 were randomized in a 1:1:1 ratio to cohorts 1–3, receiving PEG-IFN α 180 μ g, elebsiran 200 mg plus PEG-IFN α 180 μ g, and elebsiran 100 mg plus PEG-IFN α 180 μ g, respectively. At 24 weeks post-EOT, 51 participants completed the study (Fig. 1a). The mean (and s.d.) age of cohorts 1–3 was 44.0 (8.4) years. Among all randomized participants, 85.5% were male, 98.2% were Asian and 78.2% had negative hepatitis B e-antigen (HBeAg) status at baseline. Baseline HBsAg levels ranged from 2.02 to 3.39 log₁₀(IU ml⁻¹), with a mean (s.d.) of 2.78 (0.37) log₁₀(IU ml⁻¹). Demographic and baseline characteristics were generally balanced across cohorts 1–3 (Table 1).

From 24 November 2023 to 29 February 2024, 31 participants who completed elebsiran 100 mg and BRII-179 treatment in the previous BRII-179-835-001 study¹⁵ were enrolled to part II (cohort 4), receiving elebsiran 100 mg plus PEG-IFN α 180 μ g. The median time between completion of treatment in the BRII-179-835-001 study and enrollment into cohort 4 was 17.8 months, ranging from 13.8 to 23.7 months. One participant discontinued study interventions and withdrew prematurely (Fig. 1b). The baseline HBsAg level of all participants ($n = 77$) from the BRII-179-835-001 study who received nine doses of elebsiran plus BRII-179 is shown in Extended Data Fig. 2a, by categorization into BRII-179 anti-HBs responders or nonresponders based on peak anti-HBs titer (≥ 10 IU l⁻¹ or <10 IU l⁻¹). Among the 31 participants enrolled in this study, 19 participants were BRII-179 anti-HBs responders and 12 participants were nonresponders. Notably, approximately half of the BRII-179 anti-HBs responders (9 out of 19, 47.4%) and only one of the nonresponders had baseline HBsAg level >1,500 IU ml⁻¹, ranging from 1,514 to 6,479 IU ml⁻¹ in the BRII-179-835-001 study, indicating that BRII-179 may elicit anti-HBs responses in participants regardless of baseline HBsAg levels (Extended Data Fig. 2b). The mean (s.d.) age for cohort 4 was 50.3 (8.0) years. Among cohort 4 participants, 74.2% were male, 93.5% were Asian and 90.3% had negative HBeAg status at baseline. The mean (s.d.) baseline HBsAg was 2.45 (0.42) log₁₀(IU ml⁻¹) and was slightly higher in anti-HBs responders at 2.53 (0.45) log₁₀(IU ml⁻¹) compared with nonresponders at 2.31 (0.35) log₁₀(IU ml⁻¹); and three participants had baseline HBsAg ≤ 100 IU ml⁻¹ (one anti-HBs responder and two nonresponders). Eight participants had anti-HBs ≥ 10 IU l⁻¹ detected at the time of enrollment into cohort 4 (Table 1).

Primary efficacy outcome

Cohorts 1–3. At EOT, HBsAg loss was observed in 5 of 19 participants (26.3%) administered elebsiran 200 mg plus PEG-IFN α (cohort 2) and 6 of 18 participants (33.3%) administered elebsiran 100 mg plus PEG-IFN α (cohort 3), compared with 1 of 18 participants (5.6%) administered PEG-IFN α monotherapy (cohort 1) (Table 2). At 24 weeks post-EOT follow-up, HBsAg loss was observed in 4 of 19 participants (21.1%) in cohort 2 and 6 of 18 participants (33.3%) in cohort 3, compared with 1 of 18 participants (5.6%) in cohort 1 (Table 2). The Bayesian analysis results further supported the potential benefit of the combination therapy, demonstrating over an 85% probability of at least a 10% difference between either cohort 2 or cohort 3 and cohort 1 at EOT and at least a 5% difference between either cohort 2 or cohort 3 and cohort 1 at 24 weeks post-EOT (Table 2 and Extended Data Table 1).

HBsAg loss rate at either EOT or 24 weeks post-EOT was comparable between elebsiran 200 mg (cohort 2) and elebsiran 100 mg (cohort 3). Across the three cohorts, all participants achieving HBsAg loss at EOT or 24 weeks post-EOT had a baseline HBsAg level <1,500 IU ml⁻¹ (Supplementary Table 1).

Cohort 4 and cohort 4 subgroups. At EOT, HBsAg loss was observed in 13 of 31 participants (41.9%) in cohort 4. In the key subgroup analysis evaluating HBsAg loss rates in participants with demonstrated immunological response to previous immunization with BRII-179, HBsAg loss occurred in 11 of 19 BRII-179 anti-HBs responders (57.9%) compared with 2 of 12 nonresponders (16.7%) (Table 3). At 24 weeks post-EOT, HBsAg loss was observed in 9 of 31 participants (29.0%) in cohort 4, and by

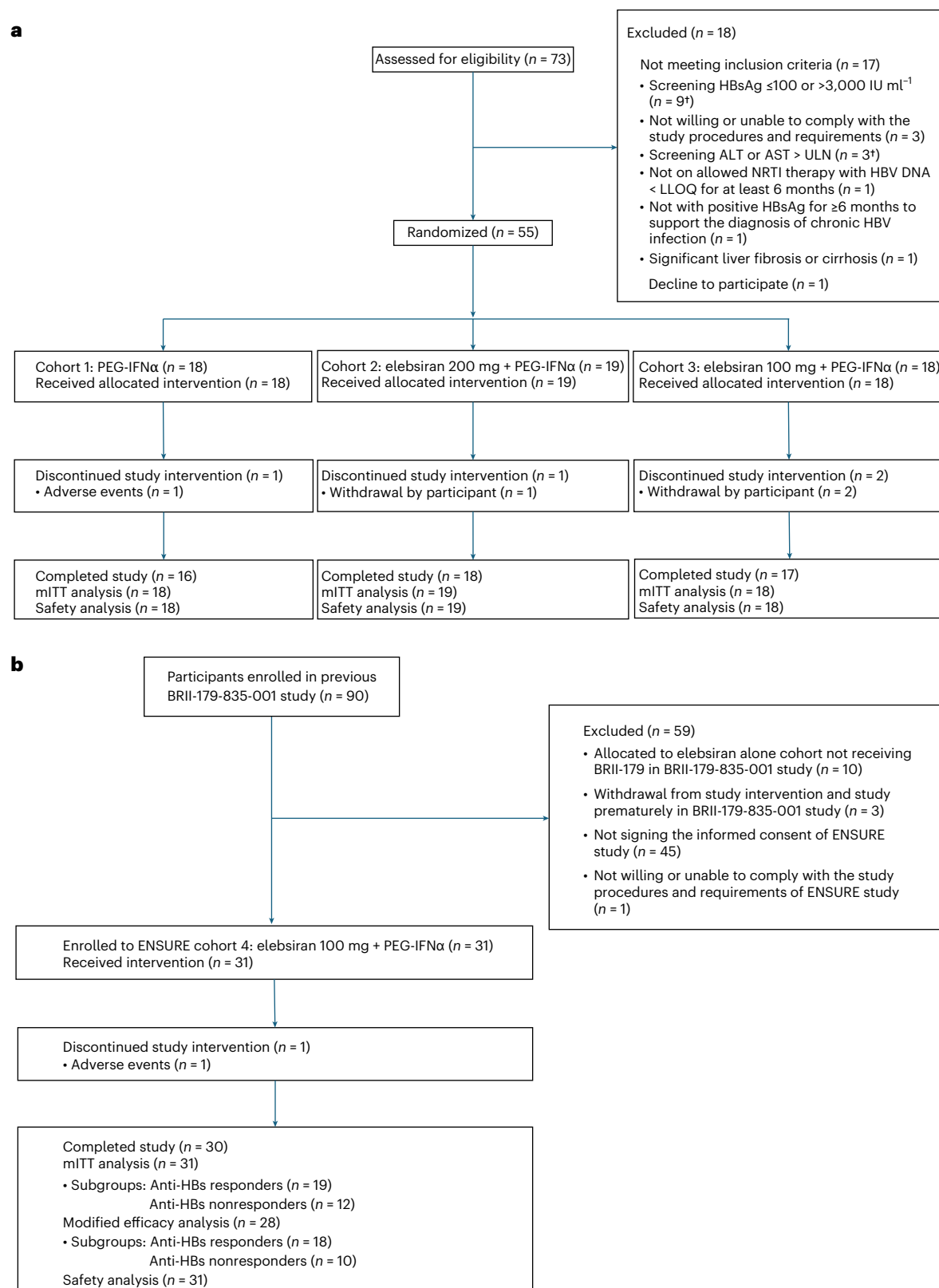


Fig. 1 | CONSORT flow diagram. a, Cohorts 1–3. The dagger indicates that one participant with ALT or AST > ULN also had HBsAg > 3,000 IU ml⁻¹. **b**, Cohort 4. The mITT (modified intention-to-treat) analysis set is defined as all participants who received at least one dose of study intervention, with at least one post-

baseline visit up to week 48. The modified efficacy analysis set is defined as all participants who had baseline HBsAg > 100 IU ml⁻¹ and received at least one dose of study intervention, with at least one post-baseline visit.

Table 1 | Demographics and baseline characteristics

	Randomized part I				Single-arm part II
	Cohort 1	Cohort 2	Cohort 3	Total	Cohort 4
	(N=18)	(N=19)	(N=18)	(N=55)	(N=31)
Age (years)					
Mean (s.d.)	45.2 (8.5)	43.5 (9.0)	43.2 (8.2)	44.0 (8.4)	50.3 (8.0)
Sex n (%)					
Male	16 (88.9)	17 (89.5)	14 (77.8)	47 (85.5)	23 (74.2)
Female	2 (11.1)	2 (10.5)	4 (22.2)	8 (14.5)	8 (25.8)
Race n (%)					
Asian	18 (100)	18 (94.7)	18 (100)	54 (98.2)	29 (93.5)
White	0	0	0	0	1 (3.2)
Other	0	1 (5.3)	0	1 (1.8)	1 (3.2)
BMI at baseline (kg m ⁻²)					
Mean (s.d.)	24.3 (3.4)	23.5 (3.9)	23.8 (2.5)	23.9 (3.3)	24.4 (3.2)
HBsAg (log ₁₀) at baseline (IU ml ⁻¹)					
Mean (s.d.)	2.80 (0.39)	2.75 (0.41)	2.80 (0.34)	2.78 (0.37)	2.45 (0.42)
Min, max	2.07, 3.39	2.02, 3.35	2.15, 3.38	2.02, 3.39	1.53, 3.34
HBsAg (IU ml ⁻¹) category at baseline n (%)					
≤100	0	0	0	0	3 (9.7)
>100 to ≤500	7 (38.9)	8 (42.1)	7 (38.9)	22 (40.0)	17 (54.8)
>500- to ≤1,500	8 (44.4)	8 (42.1)	8 (44.4)	24 (43.6)	10 (32.3)
>1,500 to ≤3,000	3 (16.7)	3 (15.8)	3 (16.7)	9 (16.4)	1 (3.2)
Anti-HBs (IU l ⁻¹) category at baseline n (%)					
<2	17 (94.4)	19 (100)	18 (100)	54 (98.2)	22 (71.0)
2 to <10	0	0	0	0	1 (3.2)
≥10	1 (5.6)	0	0	1 (1.8)	8 (25.8)
ALT at baseline (U l ⁻¹)					
Mean (s.d.)	18.2 (7.1)	20.0 (5.8)	22.2 (7.7)	20.1 (7.0)	20.5 (8.9)
HBeAg at baseline n (%)					
Negative	15 (83.3)	16 (84.2)	12 (66.7)	43 (78.2)	28 (90.3)
Positive	3 (16.7)	3 (15.8)	6 (33.3)	12 (21.8)	3 (9.7)

Analyses were conducted in the full analysis set.

subgroup, HBsAg loss occurred in 8 of 19 BR11-179 anti-HBs responders (42.1%) compared with 1 of 12 nonresponders (8.3%) (Table 3). All participants who achieved sustained HBsAg loss at 24 weeks post-EOT in cohort 4 had a baseline HBsAg level <1,500 IU ml⁻¹ at the beginning of the ENSURE study (Supplementary Table 2). However, it is noteworthy that four out of eight participants (50.0%) in cohort 4 who were BR11-179 anti-HBs responders and achieved sustained HBsAg loss had baseline HBsAg levels exceeding 1,500 IU ml⁻¹ (range 1,514–3,086 IU ml⁻¹) when enrolled in the previous BR11-179-835-001 study. A modified efficacy analysis was also conducted for cohort 4, excluding the three participants with baseline HBsAg levels ≤100 IU ml⁻¹. This analysis yielded a comparable result (Extended Data Table 2).

Across cohorts 1–4, all participants who achieved HBsAg loss at 24 weeks post-EOT met the predefined NRTI discontinuation criteria (Methods) and entered a 24-week NRTI discontinuation monitoring period, except for one participant from cohort 3, who was excluded due to HBeAg positivity.

Key secondary efficacy outcomes

Serum HBsAg and change from baseline over time. Cohorts 1–3. Throughout both the treatment and follow-up periods, a higher proportion of participants receiving elbasiran plus PEG-IFNα (cohorts 2

and 3) achieved greater reductions in HBsAg levels and higher rates of HBsAg loss compared with those receiving PEG-IFNα monotherapy (cohort 1). Among the 18 participants in cohort 1, 7 and 5 participants (38.9% and 27.8%) achieved HBsAg <100 IU ml⁻¹ and <10 IU ml⁻¹, respectively, at week 48, and 6 and 2 participants (33.3% and 11.1%) maintained these levels at week 72. By contrast, most participants in cohorts 2 and 3 achieved HBsAg <100 IU ml⁻¹ and <10 IU ml⁻¹ at week 48: 17 of 19 (89.5%) and 12 of 19 (63.2%), respectively, in cohort 2, and 14 of 18 (77.8%) and 14 of 18 (77.8%), respectively, in cohort 3. At week 72, HBsAg levels of <100 IU ml⁻¹ and <10 IU ml⁻¹ were observed in 12 of 19 (63.2%) and 5 of 19 (26.3%), respectively, in cohort 2, and 13 of 18 (72.2%) and 8 of 18 (44.4%), respectively, in cohort 3 (Fig. 2a).

The mean change from baseline in serum HBsAg level through week 72 was substantially greater ($P < 0.05$; Extended Data Table 3) in cohorts 2 and 3 compared with cohort 1 (Fig. 2c), indicating enhanced HBsAg decline with elbasiran and PEG-IFNα.

Cohort 4 and cohort 4 subgroups. By week 48, 13 of 31 participants (41.9%) achieved HBsAg loss at the EOT, with 11 of these (84.6%) reaching this endpoint within the first 24 weeks of the 48-week treatment period (Fig. 2b). BR11-179 anti-HBs responders achieved higher reductions in HBsAg levels and rates of HBsAg loss compared with nonresponders.

Table 2 | Cohorts 1–3 participants with HBsAg loss at EOT and 24 weeks post-EOT

	Cohort 1 (N=18)	Cohort 2 (N=19)	Cohort 3 (N=18)
Participants with HBsAg loss at EOT, n (%)	1 (5.6)	5 (26.3)	6 (33.3)
Point estimate of response, % (95% CrI)	5.4 (0.1, 18.1)	26.2 (10.3, 45.4)	33.3 (17.1, 49.5)
Participants with HBsAg loss at 24 weeks post-EOT, n (%)	1 (5.6)	4 (21.1)	6 (33.3)
Point estimate of response, % (95% CrI)	5.4 (0.1, 18.1)	20.8 (7.1, 38.7)	32.6 (15.0, 50.8)

The analysis was conducted in the mITT set. The point estimate of response and 95% credible interval (CrI) were calculated on the basis of the Bayesian analysis model.

At week 48, 24 of 31 participants (77.4%) reached HBsAg levels below 10 IU ml⁻¹. At week 72, approximately half of participants (15 out of 31, 48.4%) maintained at this level (Fig. 2b). Subgroup analysis revealed that 12 of 19 participants (63.2%) of BR11-179 anti-HBs responders maintained HBsAg levels <10 IU ml⁻¹ at week 72, compared with only 3 of 12 participants (25.0%) in the nonresponders (Fig. 2b).

Interestingly, BR11-179 anti-HBs responders appeared to experience greater and more rapid HBsAg loss and reductions compared with both BR11-179 anti-HBs nonresponders and those in cohorts 2 and 3 naive to BR11-179 (Fig. 2a–c and Extended Data Fig. 3), suggesting that the immunological modification or priming may impact not only the magnitude but also the timing of HBsAg loss.

Relationship between HBsAg seroconversion at EOT and sustained HBsAg loss at 24 weeks post-EOT

During the 24-week follow-up period after treatment, HBsAg rebound was observed across all cohorts in which participants received elebsiran and PEG-IFNα (Fig. 2d,e).

Across cohorts 1–3, 12 participants achieved HBsAg loss at EOT. Among them, ten (83.3%) also achieved HBsAg seroconversion, defined as HBsAg loss and anti-HBs titer ≥10 IU l⁻¹, and eight (66.7%) had anti-HBs titer ≥100 IU l⁻¹ at EOT. Among these eight participants with anti-HBs titer ≥100 IU l⁻¹ at EOT, seven (87.5%) maintained HBsAg loss at 24 weeks post-EOT. Among the two participants with anti-HBs titer between 10 IU l⁻¹ and 100 IU l⁻¹ at EOT (75 and 16 IU l⁻¹, respectively), only the participant with the higher titer sustained HBsAg loss. Notably, the two participants who did not achieve HBsAg seroconversion also sustained HBsAg loss at 24 weeks post-EOT (Fig. 2d).

In cohort 4, among the 13 participants who achieved HBsAg loss at EOT, 12 (92.3%) had HBsAg seroconversion. Eleven of the 12 participants with HBsAg seroconversion had anti-HBs titer ≥100 IU l⁻¹, including 10 participants in the anti-HBs responder group and 1 from the nonresponder group. Among the 11 participants with HBsAg loss and anti-HBs titer ≥100 IU l⁻¹ at EOT, 9 (81.8%) sustained HBsAg loss at 24 weeks post-EOT and 2 (18.2%) experienced HBsAg rebound. The other two participants who rebounded by week 72 had either no detectable anti-HBs response or anti-HBs titer <100 IU l⁻¹ at EOT (Fig. 2e). HBsAg rebound was observed in both BR11-179 anti-HBs responders and nonresponders.

Safety and tolerability

Adverse events. Most (78 of 86, 90.7%) participants experienced at least one treatment-emergent adverse event (TEAE). The incidence of TEAEs, either overall or by National Cancer Institute Common Terminology Criteria for Adverse Events grade, was generally comparable in participants receiving PEG-IFNα (cohort 1) and elebsiran plus PEG-IFNα

(cohorts 2, 3 and 4) (Table 4). Most of the TEAEs were of grade 1 or 2 in severity. Grade ≥3 TEAEs were reported in 6 of 18 participants (33.3%) in cohort 1, compared with 6 of 19 participants (31.6%) in cohort 2, 6 of 18 participants (33.3%) in cohort 3 and 5 of 31 participants (16.1%) in cohort 4 (Table 4). The most common TEAEs are summarized in Extended Data Table 4. Most TEAEs were consistent with established adverse reactions of PEG-IFNα.

In the 68 participants who received elebsiran plus PEG-IFNα in cohorts 2–4, the incidence of elebsiran-related TEAEs per cohort ranged from 32.3% (10 of 31) to 72.2% (13 of 18), while the incidence of PEG-IFNα-related TEAEs per cohort ranged from 61.3% (19 of 31) to 100% (18 of 18); the incidence of treatment-related adverse events attributed to both study interventions per cohort ranged from 22.6% (7 of 31) to 55.6% (10 of 18) (Table 4). The most common (incidence ≥10%) elebsiran-related TEAEs, including decrease in neutrophil count and platelet count and increase in liver function tests, were consistent with the most common PEG-IFNα-related TEAEs. Across cohorts 2–4, four (21.1%), five (27.8%) and four (12.9%) participants reported at least one elebsiran-related injection site reaction, respectively, all of which were grade 1 or 2 in severity. The most common elebsiran-related injection site reaction was injection site erythema.

Four serious adverse events (SAEs) were reported in 4 of 86 participants (4.7%): one seizure and one nodal marginal zone B cell lymphoma in cohort 1, one syncope in cohort 2 and one appendicitis in cohort 4. None of the four SAEs was considered related to elebsiran by the investigators; the SAEs of seizure and syncope were attributed to PEG-IFNα, while the other two were deemed unrelated to either elebsiran or PEG-IFNα (Table 4). All SAEs were resolved except for the participant diagnosed with lymphoma who withdrew from the study prematurely.

Laboratory abnormalities. Overall, the incidence of alanine aminotransferase (ALT) elevations was comparable between participants administered PEG-IFNα (cohort 1: 15 of 18, 83.3%) and elebsiran plus PEG-IFNα (cohort 2: 15 of 19, 78.9%; cohort 3: 16 of 18, 88.9%; cohort 4: 27 of 31, 87.1%). Most of the ALT increases were grade 1 or 2 in severity. ALT increases of grade 3 were observed in 2 of 19 (10.5%) of cohort 2 and 5.6% (1 of 18) of cohort 3 participants (Extended Data Table 5). These three participants did not have evidence of liver decompensation, and their ALT levels returned to normal by week 72. No participants had ALT or aspartate aminotransferase (AST) >10× upper limit of normal (ULN), total bilirubin >2× ULN or alkaline phosphatase >1.5× ULN.

Table 3 | Cohort 4 participants with HBsAg loss at EOT and 24 weeks post-EOT

	Cohort 4 (N=31)	Cohort 4 subgroups	
		BR11-179 anti-HBs responders (N=19)	BR11-179 anti-HBs nonresponders (N=12)
Participants with HBsAg loss at EOT, n (%)	13 (41.9)	11 (57.9)	2 (16.7)
Point estimate of response, % (95% CrI)	42.2 (25.4, 58.9)	57.4 (36.6, 78.3)	19.2 (1.8, 39.7)
Participants with HBsAg loss at 24 weeks post-EOT, n (%)	9 (29.0)	8 (42.1)	1 (8.3)
Point estimate of response, % (95% CrI)	29.7 (14.8, 45.4)	42.6 (21.7, 63.5)	11.5 (0.1, 28.5)

Anti-HBs responder was defined as peak anti-HBs titer ≥10 IU l⁻¹ by week 44 after nine doses of BR11-179 in the BR11-179-835-001 study. The analysis was conducted on the mITT set. The point estimate of response and 95% CrI were calculated on the basis of the Bayesian analysis model.

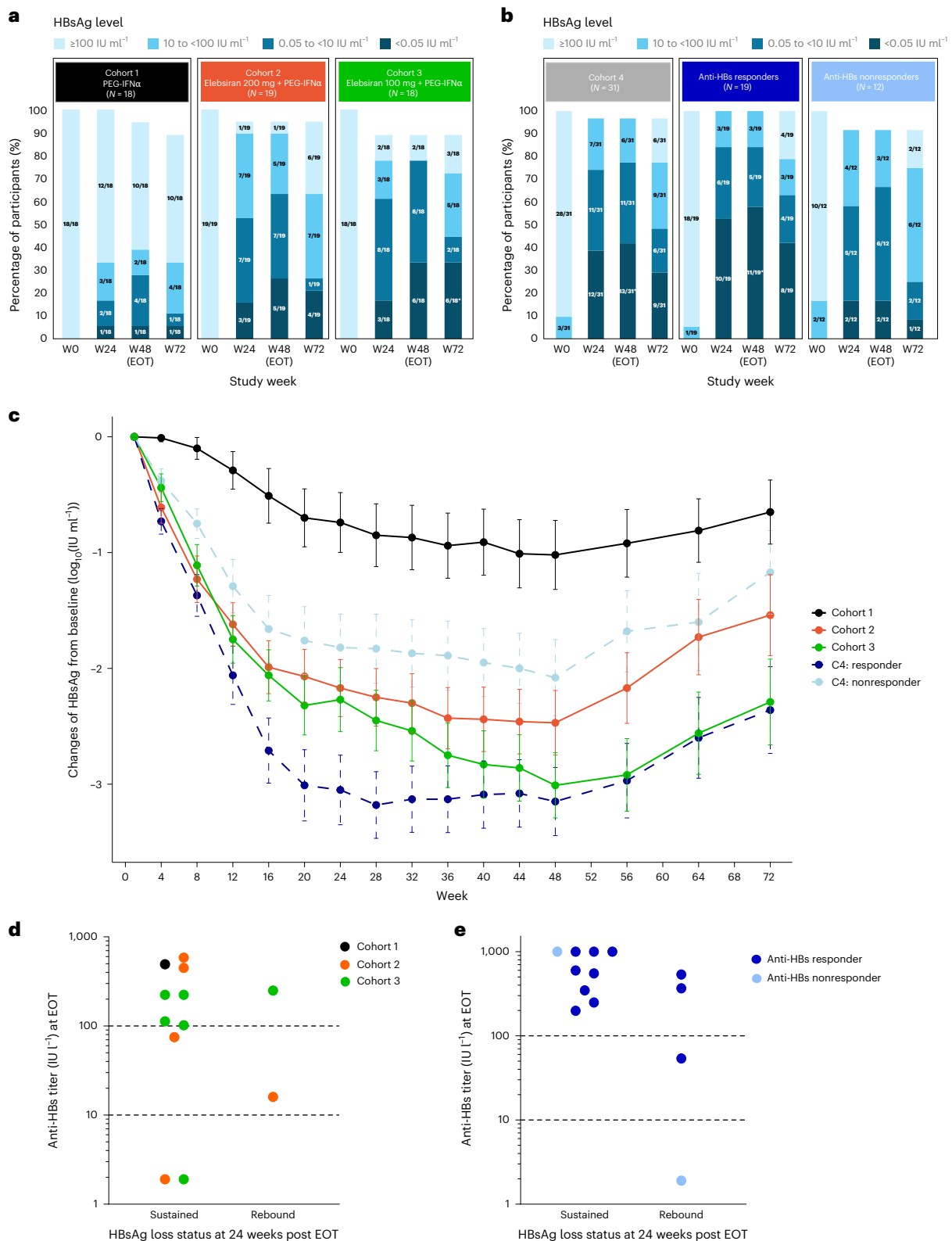


Fig. 2 | HBsAg levels and anti-HBs titers. **a**, HBsAg level in participant by study visit in cohorts 1–3. The asterisk indicates that, in cohort 3, one participant who achieved HBsAg loss at week 48 (EOT) experienced HBsAg rebound after EOT, while another participant achieved HBsAg loss at week 56 (8 weeks post-EOT), which was sustained through week 72. **b**, HBsAg level in participant by study visit in cohort 4. The asterisk indicates that, in cohort 4 (BR11-179 anti-HBs responder group), one participant had HBsAg levels <0.05 IU ml^{-1} at week 24 but experienced a rebound before week 48, while two additional participants achieved HBsAg loss between week 24 and week 48. **c**, Mean (s.e.m.) HBsAg

change from baseline through week 72 from the mITT set. The error bars represent s.e.m. Cohort 1, $N = 18$; cohort 2, $N = 19$; cohort 3, $N = 18$; cohort 4 (C4) responder, $N = 19$; C4 nonresponder, $N = 12$. **d**, The relationship between anti-HBs titer at the EOT and sustained HBsAg loss at 24 weeks post-EOT in cohorts 1–3. The dashed line represents anti-HBs levels of 10 and 100 IU l^{-1} . **e**, The relationship between anti-HBs titer at the EOT and sustained HBsAg loss at 24 weeks post-EOT in cohort 4 subgroups. The dashed line represents anti-HBs levels of 10 and 100 IU l^{-1} . Anti-HBs responder was defined as peak anti-HBs titer >10 IU l^{-1} by week 44 after nine doses of BR11-179 in the BR11-179-835-001 study.

Table 4 | Safety summary

	Cohort 1 (N=18)	Cohort 2 (N=19)	Cohort 3 (N=18)	Cohort 4 (N=31)
	n (%)	n (%)	n (%)	n (%)
Any TEAEs	18 (100)	18 (94.7)	18 (100)	24 (77.4)
Grade 1	18 (100)	18 (94.7)	18 (100)	22 (71.0)
Grade 2	15 (83.3)	16 (84.2)	15 (83.3)	14 (45.2)
Grade 3	6 (33.3)	6 (31.6)	5 (27.8)	5 (16.1)
Grade 4	2 (11.1)	0	1 (5.6)	0
Treatment-related TEAEs	17 (94.4)	18 (94.7)	18 (100)	20 (64.5)
Elebsiran related	NA	10 (52.6)	13 (72.2)	10 (32.3)
PEG-IFN α related	17 (94.4)	18 (94.7)	18 (100)	19 (61.3)
Both elebsiran and PEG-IFN α related	NA	9 (47.4)	10 (55.6)	7 (22.6)
SAEs	2 (11.1)	1 (5.3)	0	1 (3.2)
Elebsiran related	NA	0	0	0
PEG-IFN α related	1 (5.6)	1 (5.3)	0	0
Both elebsiran and PEG-IFN α related	NA	0	0	0
TEAEs leading to deaths	0	0	0	0
TEAEs leading to discontinuation of study intervention	1 (5.6)	0	0	1 (3.2)
Leading to elebsiran discontinuation	NA	0	0	0
Leading to PEG-IFN α discontinuation	1 (5.6)	0	0	1 (3.2)
TEAEs leading to discontinuation from study	1 (5.6)	0	0	1 (3.2)

The analysis was conducted on the safety analysis set. NA, not applicable.

Across the cohorts, 78 of 86 participants (90.7%) had neutrophil count decreases; the incidence was similar comparing cohort 1 versus cohort 2, 3 or 4. Neutrophil count decreases of grade ≥ 3 were observed in 7 of 18 participants (38.9%) in cohort 1, 7 of 19 participants (36.8%) in cohort 2, 4 of 18 participants (22.2%) in cohort 3 and 10 of 31 participants (32.3%) in cohort 4 (Extended Data Table 5). Platelet decreases were observed in 53 of 86 participants (61.6%), with a similar incidence across all cohorts. Platelet decreases of grade ≥ 3 occurred in 1 of 19 participants (5.3%) in cohort 2 and 1 of 18 participants (5.6%) in cohort 3 (Extended Data Table 5). No bleeding episodes were reported.

Alpha fetoprotein (AFP) elevation ($>20 \mu\text{g l}^{-1}$) was observed at the EOT in 4 of 19 participants (21.1%) in cohort 2, 6 of 18 participants (33.3%) in cohort 3 and 6 of 31 participants (19.4%) in cohort 4, compared with 0 of 18 participants (0%) in cohort 1. AFP declined to $<20 \mu\text{g l}^{-1}$ in all these participants after the EOT (Extended Data Table 6). Serial ultrasound was prospectively conducted; no evidence of malignancy was identified.

Discussion

This randomized, PEG-IFN α -controlled study evaluates the impact of the siRNA elebsiran on achieving HBsAg loss in participants with chronic HBV infection, clearly establishing its contribution as part of a combination regimen for HBV functional cure. In addition, this study evaluated the therapeutic vaccine BR11-179 as part of a sequential treatment strategy, utilizing immunological markers to identify and select patients with a higher probability of achieving HBsAg loss on treatment. The results of this study provide important insights into both the strengths and limitations of using siRNA to suppress viral antigens and HBV-specific therapeutic vaccination to break immune tolerance within an HBV functional cure strategy.

The randomized, PEG-IFN α controlled portion of this study (cohorts 1–3) evaluated two dosing regimens of elebsiran (100 mg and 200 mg every 4 weeks) in combination with weekly PEG-IFN α , compared with PEG-IFN α alone, in virally suppressed participants with chronic HBV infection. The first key result from this study was that elebsiran, when combined with PEG-IFN α , enhanced HBsAg loss rates approximately fivefold, 24 weeks following the EOT, compared with PEG-IFN α monotherapy. Noting sample size limitations, the observed rates of HBsAg loss with the elebsiran and PEG-IFN α combination in this study were similar to those that had been previously observed in a noncontrolled study¹⁴. It is noted that the response rate in the PEG-IFN α control arm in this study is lower than what has been observed in some prospective and real-world studies, but falls within the range of expected results, and may be influenced by the small sample size. A second key finding was that all participants who achieved HBsAg loss had baseline HBsAg levels below 1,500 IU ml⁻¹, most below 1,000 IU ml⁻¹. A substrata analysis was conducted by baseline HBsAg categories, with no apparent difference observed; however, substrata sample sizes were small, limiting interpretation. This observation of a baseline HBsAg-dependent response is consistent with findings from other contemporary curative regimens, supported by outcomes from siRNA plus PEG-IFN α studies¹⁶ and phase 2 studies with the antisense oligonucleotide bepirovirose¹⁷, both of which demonstrated enhanced treatment efficacy in participants with lower baseline HBsAg levels. In addition, higher anti-HBs titers ($\geq 100 \text{ IU l}^{-1}$) were associated with a greater likelihood of sustained HBsAg loss, following completion of therapy. This association has also been reported in studies involving both PEG-IFN α monotherapy¹⁸ and elebsiran plus PEG-IFN α combination therapy¹⁴. However, the mechanisms underlying durable HBsAg loss following treatment cessation remain unclear. Notably, one participant with anti-HBs titers $\geq 100 \text{ IU l}^{-1}$ experienced virological rebound, while two others maintained HBsAg loss despite having no detectable anti-HBs responses at any time point, suggesting that additional factors may contribute to immunological control and rebound.

The second, nonrandomized portion of this study (cohort 4) was an exploratory evaluation utilizing therapeutic vaccination with BR11-179 to immunologically prime patients infected with HBV and enable categorization of patients on the basis of their ability to generate anti-HBs response to therapeutic vaccination. One of the core features of chronic HBV infection is the interplay between the HBV and the immune system, with chronic viral infection leading to immune tolerance and immune exhaustion¹⁹. BR11-179 was developed to enhance HBV-specific B cell and T cell immunity, and to combine with other HBV antiviral approaches, ultimately leading to better immunological control of the virus and higher rates of functional cure. In prior studies with BR11-179 in participants chronically infected with HBV, a majority of participants (~60%) treated with repeated immunization (up to nine doses) generated robust anti-HBs antibody responses, while approximately 40% of participants were unable to mount an effective anti-HBs response despite repeated immunization¹⁵. This differs greatly from immunization in healthy participants, when receiving three doses of prophylactic PreHevbrion vaccination, with $>90\%$ achieving neutralizing antibody titers²⁰. We postulated that the ability of patients chronically infected with HBV to mount an effective anti-HBs response, following repeated immunization with BR11-179, may be an important marker for immune fitness in those patients and could potentially predict responsiveness to curative therapy. In this sequential study design, two overlapping scenarios need to be considered: (1) treatment with BR11-179 + elebsiran ‘primes’ the immune system and allows for more robust immunological control with subsequent curative therapy, and/or (2) treatment with BR11-179 + elebsiran primarily aids in the identification and selection of patients with chronic HBV infection with more intact intrinsic immunity, who are able to mount an anti-HBs response.

The results from cohort 4 provide supportive evidence for both of these scenarios, while larger and more definitive studies are required

to further define these results. In cohort 4, HBsAg loss was observed in 11 of 19 participants (57.9%) in the BRII-179 anti-HBs responder subgroup, compared with 2 of 12 participants (16.7%) in the nonresponder subgroup. This outcome suggests that BRII-179 could be used to identify patients with a higher probability of achieving HBsAg loss, by screening anti-HBs levels following dosing. A more practical dosing and screening strategy exploring 3 months and 6 months of BRII-179 with or without elebsiran is being evaluated, in the ongoing phase 2 ENRICH and ENHANCE studies. An additional observation from cohort 4 (Extended Data Fig. 2b) was that anti-HBs responses were preferentially induced by BRII-179 in participants with baseline HBsAg levels in the prior study with a median around 1,400 IU ml⁻¹. This suggests that using immunological marker stratification following therapeutic vaccination could expand the repertoire of patients eligible for future curative regimens, with treatment options for patients with higher baseline HBsAg levels. Evidence that treatment with BRII-179 + elebsiran may be contributing to enhanced immunity against HBV comes in part from the observation of a faster decline and loss of HBsAg levels in participants who were previously treated versus those that were not (Fig. 2a,b), suggesting the possibility that the participants with prior BRII-179 treatment may be primed to respond better to the subsequent curative therapy with an improved functional cure rate. Translational immunological studies are in progress to investigate whether additional immune markers are associated with antiviral efficacy and durability.

This study has some limitations. Approximately 1.5 years, on average, elapsed between the BRII-179-835-001 study and the ENSURE study, and the impact of this gap in time is unknown. In addition, cohort 4 participants received prior treatment with BRII-179 plus elebsiran rather than BRII-179 alone, requiring further investigation as to whether the combination differs from monotherapy with respect to immune activation. It has been observed that elebsiran alone does not lead to anti-HBs titer increase and induction of PreS1/PreS2-specific CD4 T cells¹⁵; however, it cannot be fully ruled out that combination with BRII-179 may induce other responses not measured, such as changes in HBsAg set point. Other studies utilizing siRNA have shown prolonged HBsAg reduction from baseline or changes in HBsAg set point during long-term follow up^{21,22}. The ongoing ENRICH and ENHANCE phase 2 trials are designed to address these limitations. ENRICH is evaluating a sequential treatment of BRII-179 alone, followed directly by 48 weeks of elebsiran plus PEG-IFN α . ENHANCE has three cohorts, evaluating the triple combination of BRII-179 plus elebsiran and PEG-IFN α given concurrently for 48 weeks, a sequential treatment of BRII-179 plus elebsiran for 24 weeks, followed by the triple combination for 24 weeks, versus 48 weeks of PEG-IFN α monotherapy. Both ENRICH and ENHANCE are prospective studies with sequential treatments, eliminating the time gap between the BRII-179-835-001 study and the ENSURE cohort 4 study. These studies were well designed to address the questions arising from the ENSURE study and further confirm the clinical benefits observed in cohort 4.

This study provides direct evidence supporting the benefit of elebsiran, in combination with PEG-IFN α , in enhancing HBsAg clearance rates in patients with chronic HBV infection. Furthermore, this study has highlighted the possibility that utilizing the therapeutic vaccine BRII-179 can help to identify and select patients on the basis of their immunological profiling, thereby resulting in a higher probability of cure in immune-responsive patients with a broader range of HBsAg levels. To our knowledge, this represents a unique HBV treatment paradigm for patient enrichment. Follow-up studies are ongoing to further validate these findings, with the goal of increasing the proportion of patients with chronic HBV infection who are eligible for, and could benefit from, curative therapy.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions

and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-025-04049-z>.

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Methods

Study design

This ongoing, open-label, phase 2 study (NCT05970289) was initiated in August 2023 at 26 sites across 7 countries/regions in Asia-Pacific region. The study was approved by an independent ethics committee or institutional review board at each site (see ‘Ethics committees/institutional review boards that approved the study protocol’ in the Supplementary Information) and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice. All participants provided written informed consent to participate in the study before any study-specific procedures were conducted. The trial design was conducted and is reported in accordance with the protocol and statistical analysis plan (SAP), which are provided in ‘ENSURE study protocol and statistical analysis plan’ in the Supplementary Information. The study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. No computer code was used for data collection.

This study was designed to evaluate the efficacy and safety of elebsiran and PEG-IFN α combination therapy in participants with chronic HBV infection without cirrhosis receiving NRTI as background therapy. It consists of two parts:

A randomized part I (cohorts 1–3): Eligible participants were randomized at 1:1:1 to cohort 1 (48 weekly doses of PEG-IFN α 180 μ g administered subcutaneously (SC) every week (QW) starting on day 1), cohort 2 (48 doses of PEG-IFN α 180 μ g administered SC QW and 13 doses of elebsiran 200 mg administered SC every 4 weeks (Q4W), both starting on day 1) and cohort 3 (48 doses of PEG-IFN α 180 μ g administered SC QW and 13 doses of elebsiran 100 mg administered SC Q4W, both starting on day 1), using an Interactive Response Technology system. The randomization code was generated through a validated computerized system. Participants were stratified at randomization by their HBsAg level at screening (>100 to ≤ 500 IU ml $^{-1}$, >500 to $\leq 1,500$ IU ml $^{-1}$ and $>1,500$ to $\leq 3,000$ IU ml $^{-1}$).

A single-arm part II (cohort 4): Eligible participants who had completed 9 doses of elebsiran and BRII-179 approximately 1.5 years ago on average in the BRII-179-835-001 study were enrolled to cohort 4 and received 48 doses of PEG-IFN α 180 μ g administered SC QW and 13 doses of elebsiran 100 mg administered SC Q4W, both starting on day 1.

After completing the 48-week treatment period, all participants from the four cohorts continued NRTI treatment and were followed for an additional 24 weeks until week 72. At week 72, participants were assessed for eligibility to discontinue NRTI therapy. Those who met all the predefined NRTI discontinuation criteria (HBsAg $<$ lower limit of quantification (LLOQ); HBV DNA $<$ LLOQ; negative HBeAg; and ALT $\leq 2 \times$ ULN) for at least two consecutive visits at week 72 stopped NRTI and entered a 24-week NRTI discontinuation monitoring period. Participants who did not meet the criteria for NRTI discontinuation continued NRTI therapy and completed the study at week 72 (Extended Data Fig. 1).

Cohort 4 was separated into two subgroups for exploratory analysis, BRII-179 anti-HBs responders and nonresponders, based on anti-HBs titer in the BRII-179-835-001 study. BRII-179 anti-HBs responder was defined as peak anti-HBs titer ≥ 10 IU l $^{-1}$ through week 44, namely 4 weeks after the last dose of BRII-179 in the previous study. The threshold of anti-HBs titer ≥ 10 IU l $^{-1}$ and the time point of 4 weeks after last dose was selected based on its use as the standard indicator of protective immunity against HBV for preventive HBV vaccines.

Objectives and endpoints

The primary objective of the study was to evaluate the efficacy and safety of elebsiran and PEG-IFN α combination therapy in participants with chronic HBV infection. Primary endpoints were:

- (1) Proportion of participants with HBsAg loss at EOT;
- (2) Proportion of participants with HBsAg loss at 24 weeks post-EOT;
- (3) Proportion of participants with TEAEs; proportion of participants with SAEs.

Secondary objectives were to assess the antiviral activity of elebsiran and PEG-IFN α combination therapy, and to assess elebsiran pharmacokinetics exposure (endpoint: plasma concentrations of elebsiran and its metabolite at selected time points) and evaluate antidrug antibody to elebsiran (endpoint: the occurrence of antidrug antibody to elebsiran and associated titer, if positive). Key secondary endpoints reported in this Article included:

- (1) Proportion of participants with HBsAg loss at week 48;
- (2) Absolute serum HBsAg and change from baseline over time through 24 weeks post-EOT;
- (3) Proportion of participants with HBsAg seroconversion at any time point.

Key eligibility criteria

Inclusion criteria. Cohorts 1–3. Participants were eligible if they met all of the following criteria: had chronic HBV infection defined by a positive serum HBsAg for ≥ 6 months; were on NRTI therapy (entecavir, tenofovir disoproxil, tenofovir alafenamide or tenofovir amibufenamide) with HBV DNA $<$ LLOQ for at least 6 months with screening HBV DNA $<$ LLOQ, HBsAg >100 IU ml $^{-1}$ and $\leq 3,000$ IU ml $^{-1}$, and ALT and AST $\leq$ ULN; age 18–60 years old (inclusive); male and female (based on medical record), body mass index (BMI) 18–32 kg m $^{-2}$ (inclusive).

Cohort 4. Participants were eligible if they met all of the following criteria: completed BRII-179 treatment in BRII-179-835-001 study; were on NRTI therapy (entecavir, tenofovir disoproxil, tenofovir alafenamide or tenofovir amibufenamide) with HBV DNA $<$ LLOQ for at least 6 months and screening HBV DNA $<$ LLOQ, HBsAg >0.05 IU ml $^{-1}$, and ALT and AST $\leq$ ULN; age ≥ 18 years old; male and female (based on medical record); BMI 18–32 kg m $^{-2}$ (inclusive).

Exclusion criteria. Participants were excluded if they met any of the following criteria: received siRNA, antisense oligonucleotide or interferon within 12 months before screening; received any HBV therapeutic vaccines before screening for cohorts 1–3; clinically important liver fibrosis or cirrhosis defined as liver stiffness >9 kPa at screening; history of drug or alcohol abuse; history of clinically meaningful chronic liver disease other than chronic HBV infection; history of hepatic decompensation; diagnosed or suspected hepatocellular carcinoma; history of uncontrolled thyroid disease, immunological function impairment, uncontrolled diabetes/hypertension, advanced-stage heart failure, psychiatric condition, cancer; current or past infection of human immunodeficiency virus, hepatitis C virus or hepatitis D virus; renal impairment defined as estimated glomerular filtration rate ≤ 60 ml min $^{-1}$ 1.73 m $^{-2}$; any laboratory test abnormalities that may contradict treatment with PEG-IFN α ; intolerance or hypersensitivity to interferon or siRNA/GalNAc.

Full eligibility criteria are listed in ‘ENSURE study protocol and statistical analysis plan’ in the Supplementary Information.

Assessments

Blood samples for quantitative HBsAg assessment that served the evaluation of primary efficacy endpoints, were collected at each visit except for week 2. Blood samples for quantitative anti-HBs assessment were collected at screening, predose day 1, weeks 16, 24, 32, 40, 48, 56, 64 and 72, or visit of EOT and/or end of study (EOS). Blood samples for quantitative HBV DNA assessment were collected at screening, predose day 1, weeks 12, 24, 36, 48, 56 and 72, or visit of EOT and/or EOS. Blood samples for qualitative HBeAg and hepatitis B e antibody (anti-HBe) assessment were collected at predose day 1, weeks 16, 32, 48 and 72, or visit of EOT and/or EOS. Qualitative HBeAg assessments at visits after day 1 were performed only for participants with positive baseline HBeAg. All abovementioned virology assessments served the evaluation of antiviral activity secondary endpoints.

Virology assessments included quantitative measurement of serum HBsAg (Cobas, ELECSYS HBsAg II quant II (Roche); LLOQ:

0.05 IU ml⁻¹), serum HBV DNA (Cobas, Cobas HBV kit (COBAS); LLOQ: 10 IU ml⁻¹), anti-HBs (Cobas, ELECSYS anti-HBs (Roche); LLOQ: 2.0 IU l⁻¹); and qualitative measurements of serum HBeAg (Cobas, ELECSYS HBeAg (Roche)), anti-HBe (Cobas, ELECSYS anti-HBe (Roche)).

Primary safety endpoints were TEAEs and SAEs that were collected through the study with information on such as severity and causal relationship with study intervention(s). Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 and graded by the investigators according to CTCAE version 5.0. Other safety assessments in the study included incidence and magnitude of abnormal findings from laboratory tests, physical examination, vital signs, liver stiffness and ultrasound, which were conducted through the study per scheduled assessment.

All laboratory tests were performed by central laboratories from IQVIA Laboratories (formerly Q Squared Solutions Beijing) in Beijing for sites of China mainland and IQVIA Laboratories Asia Pte. Ltd (formerly Q Squared Solutions Pte Ltd) in Singapore for sites of the Asian-Pacific region.

Statistical methods

Up to 75 participants were planned to be randomized in a 1:1:1 ratio across cohorts 1–3. The actual sample size was informed by a Bayesian statistical model. Specifically, with 15 participants per cohort, the lower bounds of the 95% CrI would exclude a response rate of 10%, provided the observed response rate was greater than 27%. The post probability of true response rate > 0.15 is more than 90%. Up to 45 participants were to be enrolled in cohort 4, and no formal sample size was calculated. No formal statistical interim monitoring for sample size adjustment was planned.

All participants assigned to study intervention will be included in the full analysis set. The safety analysis set included all participants assigned to study intervention and who received at least one dose of study intervention. The safety analyses included descriptive summaries of adverse event incidence and laboratory data.

The mITT analysis set was defined as all participants assigned to the study intervention who received at least one dose and had at least one post-baseline visit through week 48. The modified efficacy analysis set was defined as all participants who had baseline HBsAg > 100 IU ml⁻¹ and received at least one dose of study intervention, with at least one post-baseline visit through week 48. The efficacy analysis was performed within the mITT analysis set. Participants of cohort 4 were also analyzed on the basis of the modified efficacy analysis set as a supplementary analysis.

For the primary efficacy endpoints, an estimation approach with no hypothesis testing was used for analysis. A Bayesian hierarchical model was used as the primary analysis to estimate the posterior probability of the response rate for each of cohorts 1–3, incorporating the screening HBsAg level as a stratification factor. The point estimate of the primary outcome and 95% equal-tailed CrI were drawn from the model. The posterior distribution of the group-level response rate was derived using a mixture of the posterior distributions of response rate for each analysis stratum in that group. The weights were proportional to the sample size of each stratum. Samples from the posterior distribution of response rates in each of cohorts 1–3 were used to calculate posterior probabilities of interest—for example, the probability that the difference in the proportion achieving the primary endpoint between two cohorts exceeds a given threshold. Thresholds such as 5%, 10%, 15%, 20% or other percentiles of interest were explored. For cohort 4, an unstratified Bayesian estimation was conducted as no stratification factor was planned in this cohort. For cohorts 1–3, changes from baseline in HBsAg (on a log₁₀ scale) at all scheduled visits were statistically analyzed using a mixed model for repeated measures. No formal statistical testing was planned.

SAS version 9.4 was used for data analyses in this study.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Study protocol and statistical analysis plan are available in ‘ENSURE Study Protocol and Statistical Analysis Plan’ in the Supplementary Information. Owing to the ongoing nature of the ENSURE study, the deidentified individual participant data that underlie the results reported in this Article will be shared on request, or after the completion of the trial within the timeframe as required by ClinicalTrials.gov (NCT05970289). Study completion is expected in the second half of 2026. For inquiries, the contact person is Z.H. Source data are provided with this paper.

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Author contributions

Z.H., Q.Z., Xiaofei Chen and C.Z. contributed to the overall conception or design of the study. J.J., Q.X. and Xinyue Chen were involved in the design of part I of this study, and G.L.-H.W. and M.-F.Y. contributed to the design of part II of this study and data interpretation. G.L.-H.W., M.-F.Y., B.L., M.W.D., P.H., Q.X., F.L., W.Y.T., A.L., D.J.K., P.T., Y.-S.L., C.-Y.D., J.O., M.W., S.K., T.P., W.M., Xinyue Chen, C.-J.L., J.H., J.L., J.N., Rahul Kumar and Rajneesh Kumar were study investigators and contributed to data acquisition. C.Z., K.C., A.T., Xiaofei Chen, Q.Z., D.M. and Z.H. contributed to data analysis and/or interpretation. All authors revised the manuscript critically for important intellectual content and approved the final version for publication.

Competing interests

G.L.-H.W. is receiving a research grant from Gilead Sciences and is an advisory committee member of AstraZeneca, Barinthus Biotherapeutics, Gilead Sciences, GlaxoSmithKline, Janssen and Virion, as well as speaker of Abbott, AbbVie, Bristol-Myers Squibb, Echosens, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen and Roche. M.-F.Y. is advisor/consultant for and/or having received grant support from Aligos Therapeutics, Arbutus Biopharma, Argo Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Ausperbio Therapeutics, Bii Bioscience, Barthinus Biotherapeutics, Clear B Therapeutics, Dicerna Pharmaceuticals, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Pfizer, Precision BioSciences, Primmune Therapeutics, Immunocore, Janssen, Roche, Silverback Therapeutics, Sysmex Corporation, Tune Therapeutics and Vir Biotechnology. M.W.D. received grants from Gilead Sciences, is advisor for Gilead Sciences and GlaxoSmithKline and is speaker of GlaxoSmithKline and Roche. Y.-S.L. receives grant and payment of

consulting and expert testimony from Gilead Sciences, is a speaker of Gilead Sciences and is a DSMB and/or advisory board member of Gilead Sciences and Vaccitech. T.P. is receiving grant/research from Roche Diagnostic, Janssen, VIR, GSK and Sysmex and is an advisory board member of Aligos and speaker of Roche, VIATRIS, Eisai, AstraZeneca and Sysmex. J.H. received grant support from Gilead and Roche, is a consultant of Roche and BMS and is a speaker of AbbVie Korea, Roche, Yuhan Korea, Oncolys and Gilead and a steering committee member of AstraZeneca. C.Z., K.C., A.T., Xiaofei Chen, Q.Z., D.M. and Z.H. are employees and hold stock and options in Bii Biosciences. All other authors declare no competing interests.

Additional information

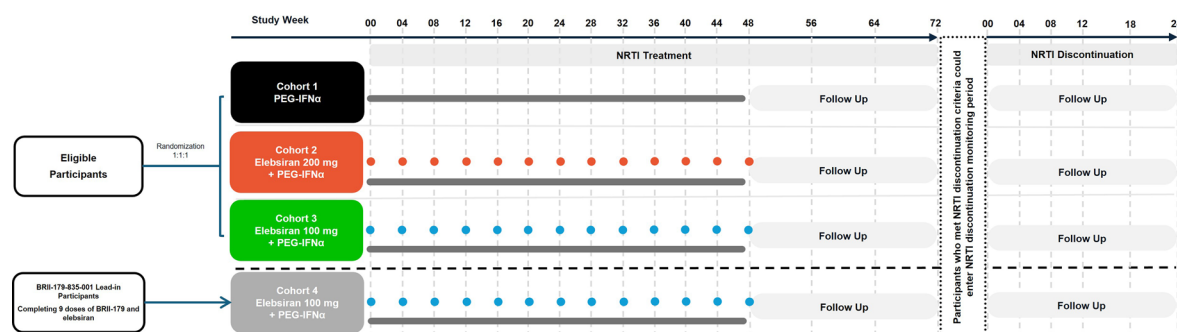
Extended data is available for this paper at <https://doi.org/10.1038/s41591-025-04049-z>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-025-04049-z>.

Correspondence and requests for materials should be addressed to Jidong Jia or Zhi Hong.

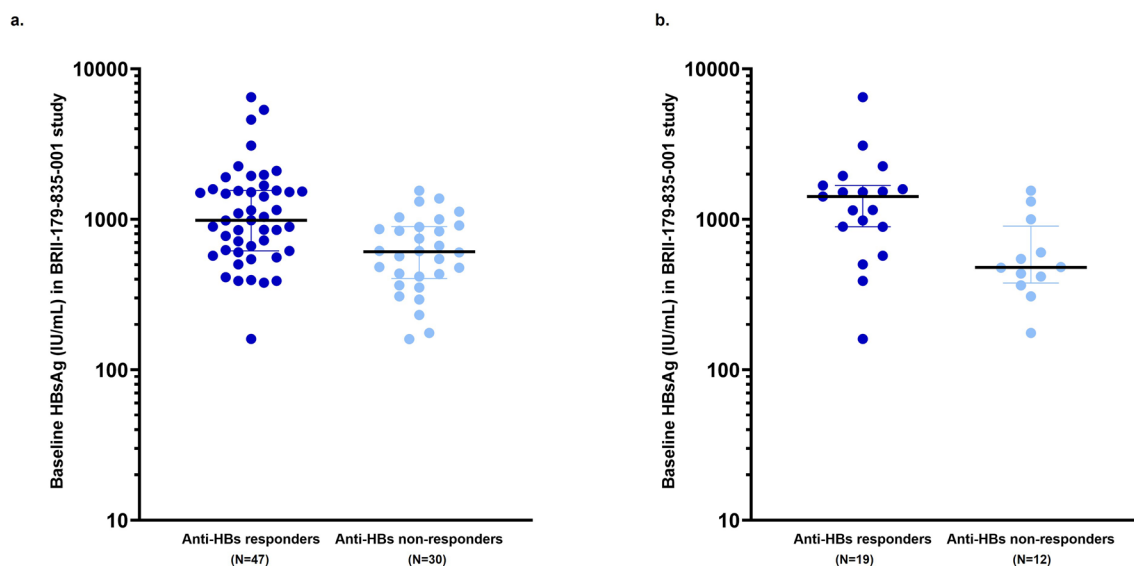
Peer review information *Nature Medicine* thanks Jordan J. Feld and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Ashley Castellanos-Jankiewicz, in collaboration with the *Nature Medicine* team.

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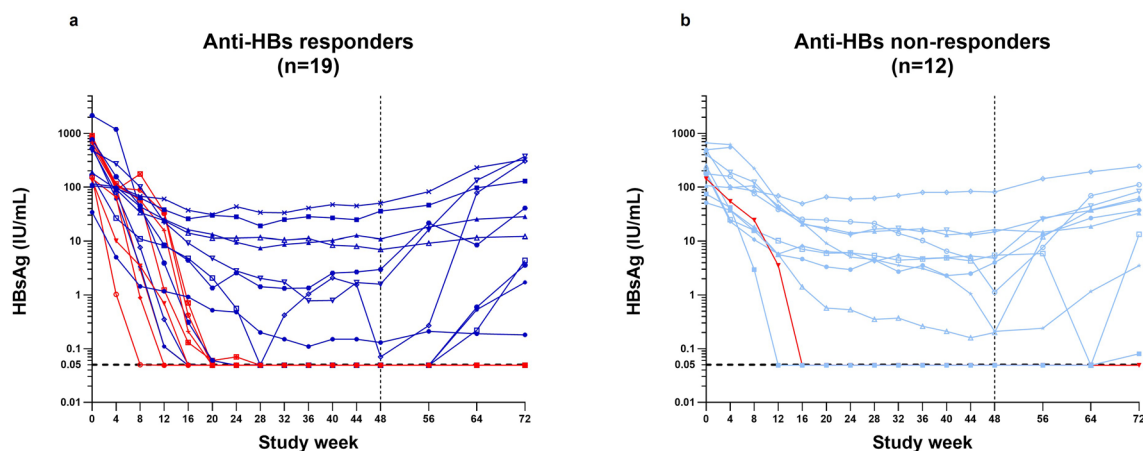
Extended Data Fig. 1 | ENSURE Study Schema. Gray solid lines represent PEG-IFNα 180 µg subcutaneous weekly administration for 48 doses, closed circles represent elebsiran 200 mg (orange) and 100 mg (blue) administered subcutaneously every 4 weeks for 13 doses. Randomization for Cohorts 1-3 was stratified by screening HBsAg levels of the eligible participants. Upon completion

of dosing, all participants were maintained on NRTI therapy for 24 weeks. Those who met the predefined criteria for NRTI discontinuation subsequently entered a 24-week monitoring period, during which all medications were withdrawn. NRTI, nucleos(t)ide reverse transcriptase inhibitor.



Extended Data Fig. 2 | Baseline HBsAg level in BR11-179-835-001 study participants by subgroups. Baseline HBsAg level in **a**, all BR11-179-835-001 study participants receiving 9 doses of elebsiran + BR11-179 (n = 77). **b**, a subset of BR11-179-835-001 study participants enrolled in ENSURE Cohort 4 (n = 31). Dark

blue dots indicate BR11-179 anti-HBs responders; light blue dots indicate BR11-179 anti-HBs non-responders. Horizontal lines indicate summary statistics: Thick horizontal lines represent the median values, while thin horizontal lines denote the first (Q1) and third (Q3) quartiles.



Extended Data Fig. 3 | Individual serum HBsAg over time in BR11-179 anti-HBs responders (a) and anti-HBs non-responders (b). Serum HBsAg levels over time in each individual participant from Cohort 4 are presented grouped by BR11-179 anti-HBs responders and anti-HBs non-responders. The red line represents

participants who achieved sustained HBsAg loss at 24 weeks post EOT. The horizontal dashed line represents the LLOQ of quantitative HBsAg assay (0.05 IU/mL). The vertical dashed line represents the EOT (Week 48). LLOQ, lower limit of quantification; EOT, end of treatment.

Extended Data Table 1 | Probability of success estimated based on HBsAg loss at EOT and 24 weeks post-EOT – Cohorts 1-3

Cohort	N	HBsAg Loss at EOT n (%)	Difference between Cohorts (%)		Threshold	Probability (Difference > Threshold) (%)	
			C3 - C1	C2 - C1		C3 - C1	C2 - C1
At EOT							
1	18	1 (5.6)	27.8	20.8	5%	98.8	94.3
2	19	5 (26.3)			10%	96.4	85.1
3	18	6 (33.3)			15%	91.1	70.5
24 Weeks Post-EOT							
1	18	1 (5.6)	27.8	15.5	5%	98.3	87.1
2	19	4 (21.1)			10%	95.1	71.5
3	18	6 (33.3)			15%	87.9	50.6

Bayesian hierarchical model incorporating the screening HBsAg level stratification factor (>100 - ≤500 IU/mL, >500 - ≤1,500 IU/mL and >1,500 - ≤3,000 IU/mL) was used to estimate the probability of success. The analysis was conducted in the mITT set. C, Cohort; EOT, end of treatment.

Extended Data Table 2 | Cohort 4 participants with HBsAg loss at EOT and 24 weeks post-EOT in modified efficacy population

	Cohort 4 (N=28)	Cohort 4 Subgroups	
		BRIL-179 Anti-HBs Responders (N=18)	BRIL-179 Anti-HBs Non-responders (N=10)
Participants with HBsAg loss at EOT, n (%)	12 (42.9)	11 (61.1)	1 (10.0)
Participants with HBsAg loss at 24 weeks post-EOT, n (%)	9 (32.1)	8 (44.4)	1 (10.0)

BRIL-179 anti-HBs responder was defined as peak anti-HBs titer ≥ 10 IU/L by Week 44 after 9 doses of BRIL-179 in BRIL-179-835-001 study. The analysis was conducted in the modified efficacy analysis set defined as all participants who had baseline HBsAg levels >100 IU/mL and received at least 1 dose of study intervention, with at least 1 post-baseline visit. EOT, end of treatment.

Extended Data Table 3 | Serum HBsAg log10 (IU/mL) and change from baseline over time through Week 72 in Cohorts 1-3

	Baseline Mean (SD)	Week 72 Mean (SD)	Cohort 3 - Cohort 1		Cohort 2 - Cohort 1	
			LSMD (95% CI)	p-value	LSMD (95% CI)	p-value
Cohort 1	2.80 (0.39)	2.17 (1.20)	-1.58 (-2.25, -0.90)	<0.0001	-0.86 (-1.53, -0.18)	0.0145
Cohort 2	2.75 (0.41)	1.18 (1.55)				
Cohort 3	2.80 (0.34)	0.51 (1.70)				

The analysis was conducted in the mITT set. LSMD: least squares mean difference; CI: confidence interval; SD, standard deviation. The difference of change from baseline to Week 72 in HBsAg (log base 10 scale) was analyzed using a Mixed Model for Repeated Measures. In this model log base 10 scale HBsAg baseline as a covariate, cohort, visit, cohort by visit as fixed effects, and within-participant errors were modelled with a heterogeneous autoregressive (1) variance matrix.

Extended Data Table 4 | Summary of TEAEs reported in ≥10% participants by SOC and PT

SOC PT	Cohort 1 (N=18) n (%)	Cohort 2 (N=19) n (%)	Cohort 3 (N=18) n (%)	Cohort 4 (N=31) n (%)	Study Total (N=86) n (%)
General disorders and administration site conditions					
Pyrexia	7 (38.9)	5 (26.3)	5 (27.8)	10 (32.3)	27 (31.4)
Fatigue	2 (11.1)	4 (21.1)	2 (11.1)	5 (16.1)	13 (15.1)
Injection site erythema	3 (16.7)	4 (21.1)	1 (5.6)	5 (16.1)	13 (15.1)
Influenza like illness	3 (16.7)	5 (26.3)	1 (5.6)	1 (3.2)	10 (11.6)
Investigations					
Neutrophil count decreased	12 (66.7)	12 (63.2)	11 (61.1)	2 (6.5)	37 (43.0)
Alanine aminotransferase increased	9 (50.0)	10 (52.6)	12 (66.7)	2 (6.5)	33 (38.4)
Platelet count decreased	8 (44.4)	10 (52.6)	9 (50.0)	0	27 (31.4)
Aspartate aminotransferase increased	8 (44.4)	9 (47.4)	7 (38.9)	0	24 (27.9)
White blood cell count decreased	10 (55.6)	7 (36.8)	6 (33.3)	0	23 (26.7)
Gamma-glutamyltransferase increased	2 (11.1)	9 (47.4)	8 (44.4)	0	19 (22.1)
Alpha 1 foetoprotein increased	0	5 (26.3)	5 (27.8)	1 (3.2)	11 (12.8)
Lymphocyte count decreased	2 (11.1)	4 (21.1)	3 (16.7)	1 (3.2)	10 (11.6)
Musculoskeletal and connective tissue disorders					
Myalgia	5 (27.8)	1 (5.3)	3 (16.7)	3 (9.7)	12 (14.0)
Blood and lymphatic system disorders					
Leukopenia	1 (5.6)	2 (10.5)	6 (33.3)	1 (3.2)	10 (11.6)
Nervous system disorders					
Headache	2 (11.1)	4 (21.1)	3 (16.7)	3 (9.7)	12 (14.0)

Percentages are based on the number of participants in the cohort. The analysis was conducted in the safety analysis set. PT, preferred term; SOC, system organ class.

Extended Data Table 5 | Summary of key treatment emergent laboratory abnormalities

Maximum Postbaseline Toxicity Grade	Cohort 1 (N=18)	Cohort 2 (N=19)	Cohort 3 (N=18)	Cohort 4 (N=31)	Study Total (N=86)
ALT Increased					
Any Grade	15 (83.3)	15 (78.9)	16 (88.9)	27 (87.1)	73 (84.9)
Grade 1	13 (72.2)	12 (63.2)	11 (61.1)	25 (80.6)	61 (70.9)
Grade 2	2 (11.1)	1 (5.3)	4 (22.2)	2 (6.5)	9 (10.5)
Grade 3	0	2 (10.5)	1 (5.6)	0	3 (3.5)
Grade 4	0	0	0	0	0
AST Increased					
Any Grade	15 (83.3)	17 (89.5)	13 (72.2)	28 (90.3)	73 (84.9)
Grade 1	14 (77.8)	15 (78.9)	12 (66.7)	28 (90.3)	69 (80.2)
Grade 2	1 (5.6)	1 (5.3)	1 (5.6)	0	3 (3.5)
Grade 3	0	1 (5.3)	0	0	1 (1.2)
Grade 4	0	0	0	0	0
Total Bilirubin Increased					
Any Grade	1 (5.6)	2 (10.5)	1 (5.6)	2 (6.5)	6 (7.0)
Grade 1	1 (5.6)	2 (10.5)	1 (5.6)	2 (6.5)	6 (7.0)
Grade 2	0	0	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Neutrophils Decreased					
Any Grade	17 (94.4)	18 (94.7)	16 (88.9)	27 (87.1)	78 (90.7)
Grade 1	2 (11.1)	0	5 (27.8)	5 (16.1)	12 (14.0)
Grade 2	8 (44.4)	11 (57.9)	7 (38.9)	12 (38.7)	38 (44.2)
Grade 3	5 (27.8)	7 (36.8)	4 (22.2)	10 (32.3)	26 (30.2)
Grade 4	2 (11.1)	0	0	0	2 (2.3)
Leukocytes Decreased					
Any Grade	17 (94.4)	17 (89.5)	16 (88.9)	31 (100.0)	81 (94.2)
Grade 1	2 (11.1)	2 (10.5)	7 (38.9)	10 (32.3)	21 (24.4)
Grade 2	13 (72.2)	15 (78.9)	8 (44.4)	17 (54.8)	53 (61.6)
Grade 3	2 (11.1)	0	1 (5.6)	4 (12.9)	7 (8.1)
Grade 4	0	0	0	0	0
Platelets Decreased					
Any Grade	10 (55.6)	14 (73.7)	12 (66.7)	17 (54.8)	53 (61.6)
Grade 1	8 (44.4)	13 (68.4)	10 (55.6)	16 (51.6)	47 (54.7)
Grade 2	2 (11.1)	0	1 (5.6)	1 (3.2)	4 (4.7)
Grade 3	0	0	1 (5.6)	0	1 (1.2)
Grade 4	0	1* (5.3)	0	0	1* (1.2)

* Per investigation, pre-analytical issues could not be ruled out for the CTCAE Grade 4 result at Week 28, and the result was considered as non-clinically significant. For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant. The analysis was conducted in the safety analysis set. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Extended Data Table 6 | Summary of AFP elevation by study visit

AFP elevation (µg/L)	Cohort 1 (N=18) n (%)	Cohort 2 (N=19) n (%)	Cohort 3 (N=18) n (%)	Cohort 4 (N=31) n (%)
Baseline				
> 20	0	0	0	0
> 100	0	0	0	0
Week 48 (End of treatment)				
> 20	0	4 (21.1)	6 (33.3)	6 (19.4)
> 100	0	1 (5.3)	1 (5.6)	0
Week 72				
> 20	0	0	0	0
> 100	0	0	0	0

The analysis was conducted in the safety analysis set. AFP, alpha fetoprotein.

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☐	☒ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated

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Software and code

Policy information about [availability of computer code](#)

Data collection	No computer code was used for data collection.
Data analysis	SAS Version 9.4 was used for data analyses.

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Study protocol and statistical analysis plan are available in Supplementary Information, 'ENSURE Study Protocol and Statistical Analysis Plan'. Due to the ongoing nature of the ENSURE study, the de-identified individual participant data that underlie the results reported in the article will be shared on request, or after the completion of the trial within the timeframe as required by ClinicalTrials.gov (NCT05970289). The completion of the study is expected to be in the second half of 2026. For inquiries, the contact person is Dr. Zhi Hong.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	Provided in manuscript, Table 1; participants were enrolled irrespective of their sex. Any data on sex were collected at each investigational site based on medical records. Given the limited sample size in this phase 2 study, as well as considering the lack of strong evidence indicating a difference between males and females in the disease characteristics of chronic HBV infection or in response to the study treatment, we did not prespecify a sex-based subgroup analysis to avoid drawing potentially biased conclusion that driven by chance.
Reporting on race, ethnicity, or other socially relevant groupings	Provided in manuscript, Table 1; participants were screened and enrolled irrespective of their race/ethnicity.
Population characteristics	Provided in manuscript, Table 1.
Recruitment	This ongoing, open-label study was initiated in August 2023 at 26 sites across 7 countries /regions in Asia-Pacific region; a total of 86 participants were enrolled. Recruitment involved obtaining written informed consent from all participants or their legal representatives before inclusion in the trial. The key inclusion/exclusion criteria are detailed in manuscript, methods section. There was no self-selection biases.
Ethics oversight	The study was approved by an independent ethics committee or institutional review board at each investigational site. A list of Ethics Committees that approved the protocol is provided in Supplementary Information, 'Ethics Committees / Institutional Review Boards that Approved the Study Protocol'.

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Field-specific reporting

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Up to 75 participants were planned to be randomized in a 1:1:1 ratio to each of Cohorts 1-3. The actual sample size was informed by a Bayesian statistical model. Specifically, with 15 participants per cohort, the lower bounds of the 95% credible interval (CrI) would exclude a response rate of 10%, provided the observed response rate was greater than 27%. The post probability of true response rate >0.15 is more than 90%. Up to 45 participants were to be enrolled in Cohort 4 and no formal sample size was calculated. No formal statistical interim monitoring for sample size adjustment was planned.
Data exclusions	No data were excluded from the analyses.
Replication	This is a phase 2 exploratory clinical trial; confirmatory results are not yet available at this point. Replication of the findings from this study will be conducted later.
Randomization	Participants enrolled in Cohorts 1-3 were randomly allocated to each cohort at a ratio of 1:1:1. Participants enrolled in Cohort 4 completed a previous study BR11-179-835-001 and randomization was not applicable.
Blinding	Not applicable; this was an open-label study.

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☒	☐ Eukaryotic cell lines
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☐	☒ Clinical data
☒	☐ Dual use research of concern
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Methods

n/a	Involved in the study
☒	☐ ChIP-seq
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Clinical data

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Clinical trial registration	ClinicalTrials.gov identifier: NCT05970289
Study protocol	The study protocol has been included in the submission.
Data collection	Data were collected from 22 Aug 2023 to 19 Jul 2025 at 26 study sites in Asian-Pacific region. The study and its data collection is still ongoing.
Outcomes	All the primary and secondary endpoints were predefined as detailed in the submitted protocol and SAP (Supplementary Information, 'ENSURE Study Protocol and Statistical Analysis Plan'). Outcomes up to 24 week post-EOT are summarized in this article. Clinical outcomes of functional cure and post NRTI discontinuation as well as elebsiran PK and ADA are being evaluated and will be reported separately. The primary endpoints were: 1. Proportion of participants with HBsAg loss at EOT 2. Proportion of participants with HBsAg loss at 24 weeks post-EOT 3. Proportion of participants with TEAEs; proportion of participants with SAEs The secondary endpoints were: 1. Proportion of participants with HBsAg loss at Week 48 2. Absolute serum HBsAg and change from baseline over time through 24 weeks post-EOT 3. Proportion of participants with HBsAg seroconversion at any timepoint 4. Proportion of participants achieving functional cure 5. Proportion of participants achieving HBsAg seroclearance and HBV DNA<LLOQ at 24 weeks after discontinuation of all treatments, including NRTI 6. Proportion of participants meeting NRTI discontinuation criteria at 24 weeks post EOT 7. Nadir serum HBsAg and maximum reduction of serum HBsAg from baseline throughout 48-week treatment 8. Time to achieve first serum HBsAg seroclearance through Week 72 9. Proportion of participants with HBeAg seroclearance and HBeAg seroconversion (baseline HBeAg-positive participants) at any timepoint 10. Plasma concentrations of BRII-835 and its metabolite at selected timepoints 11. The occurrence of ADA to BRII-835 and associated titer, if positive

Plants

Seed stocks	Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.
Novel plant genotypes	Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.
Authentication	Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.