ORIGINAL ARTICLE

Xalnesiran with or without an Immunomodulator in Chronic Hepatitis B

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ABSTRACT

BACKGROUND

Xalnesiran, a small interfering RNA molecule that targets a conserved region of the hepatitis B virus (HBV) genome and silences multiple HBV transcripts, may have efficacy, with or without an immunomodulator, in patients with chronic HBV infection.

METHODS

We conducted a phase 2, multicenter, randomized, controlled, adaptive, open-label platform trial that included the evaluation of 48 weeks of treatment with xalnesiran at a dose of 100 mg (group 1), xalnesiran at a dose of 200 mg (group 2), xalnesiran at a dose of 200 mg plus 150 mg of ruzotolimod (group 3), xalnesiran at a dose of 200 mg plus 180 μg of pegylated interferon alfa-2a (group 4), or a nucleoside or nucleotide analogue (NA) alone (group 5) in participants with chronic HBV infection who had virologic suppression with NA therapy. The primary efficacy end point was hepatitis B surface antigen (HBsAg) loss (HBsAg level, <0.05 IU per milliliter) at 24 weeks after the end of treatment. Safety was also assessed.

RESULTS

Among 159 participants (30, 30, 34, 30, and 35 in groups 1 through 5, respectively), the primary end-point event occurred in 7% (95% confidence interval [CI], 1 to 22) of those in group 1, in 3% (95% CI, 0 to 17) of those in group 2, in 12% (95% CI, 3 to 28) of those in group 3, in 23% (95% CI, 10 to 42) of those in group 4, and in none (95% CI, 0 to 10) of those in group 5. In groups 1 through 5, respectively, HBsAg seroconversion occurred in 3%, none, 3%, 20%, and none of the participants at 24 weeks after the end of treatment. HBsAg loss with or without seroconversion occurred only in participants with a screening HBsAg level below 1000 IU per milliliter. In groups 1 through 5, respectively, grade 3 or 4 adverse events occurred in 17%, 10%, 18%, 50%, and 6% of the participants, with the most frequent event being an elevated alanine aminotransferase level.

CONCLUSIONS

Among participants with chronic HBV infection who had virologic suppression with NA therapy, treatment with xalnesiran plus an immunomodulator resulted in HBsAg loss at 24 weeks after the end of treatment in a substantial percentage of participants. Grade 3 or 4 adverse events were not uncommon. (Funded by F. Hoffmann–La Roche; Piranga ClinicalTrials.gov number, NCT04225715.)

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

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Despite the implementation of public health strategies to reduce the global burden of chronic hepatitis B virus (HBV) infection, this disease remains a major health threat, affecting nearly 300 million persons worldwide.[1,2] Persons with chronic HBV infection are at increased risk for premature death from cirrhosis or hepatocellular carcinoma, as well as at increased risk for extrahepatic manifestations that are associated with decreased quality of life.[3-6] Functional cure (defined as a sustained loss of hepatitis B surface antigen [HBsAg] and undetectable HBV DNA at 24 weeks after finite-duration therapy) is a desired treatment outcome that is associated with significantly reduced risks of hepatocellular carcinoma, cirrhosis, liver decompensation, and death from any cause.[7,8] Standard care, which includes pegylated interferon therapy of finite duration (48 weeks) and lifelong nucleoside or nucleotide analogue (NA) therapy, rarely leads to functional cure, which occurs in only up to 7% of patients after 12 months of treatment.[9-11]

To improve functional cure rates, an emerging strategy involves combining new antiviral agents to reduce the antigenic load with immunomodulators to restore the dysregulated immune response.[12-14] Xalnesiran is an investigational *N*-acetyl-D-galactosamine–conjugated synthetic double-stranded small interfering RNA molecule that targets the S conserved region of the HBV genome, silencing multiple transcripts. In a phase 1 study, xalnesiran induced substantial and durable reductions in HBsAg levels,[15] results that supported the development of this drug as the backbone of finite-duration treatment regimens. Ruzotolimod is an investigational toll-like receptor 7 (TLR7) agonist selectively activated in the liver that is being evaluated for use in persons with chronic HBV infection.[16,17]

The phase 2 Piranga trial, a platform trial for chronic HBV infection, was set up to evaluate finite-duration combination regimens, including one or more new molecular entities. Here, we report the efficacy and safety results regarding xalnesiran regimens with or without an immunomodulator, ruzotolimod or pegylated interferon (peginterferon) alfa-2a, in persons who had virologic suppression with NA therapy.

Methods

Oversight

We conducted this trial according to the Good Clinical Practice guidelines of the International Council for Harmonisation, the principles of the Declaration of Helsinki, and all applicable laws and regulations in the participating countries. The trial protocol (available with the full text of this article at NEJM.org) was approved by independent review boards or ethics committees at each trial site. All the participants provided written informed consent.

A Quick Take is available at NEJM.org

The sponsor, F. Hoffmann–La Roche, designed and monitored the trial, provided all the investigational medicinal products free of charge, collected the data, and conducted the data analyses, which were then provided to all the authors. Manuscript drafts were prepared by the authors, with the assistance of a professional medical writer funded by the sponsor. All the authors made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the analyzed data and for the fidelity of the trial to the protocol.

Participants

Eligible participants were 18 to 65 years of age, had chronic HBV infection, and were receiving NA monotherapy (entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate) for at least 12 months before screening and receiving the same NA therapy for at least the most recent 3 months before screening. Participants had to have an HBV DNA level below 20 IU per milliliter and an alanine aminotransferase (ALT) level that was no more than 1.5 times the upper limit of the normal range (ULN) for more than 6 months before screening. Key exclusion criteria were infection with hepatitis A, C, D, or E virus or human immunodeficiency virus, clinically significant liver fibrosis or cirrhosis (fibrosis stage ≥F3 on liver biopsy or liver stiffness of ≥7.4 kPa on transient elastography), and hepatocellular carcinoma. The full inclusion and exclusion criteria are listed in the protocol.

Trial Design and Procedures

This phase 2, multicenter, randomized, controlled, adaptive, open-label platform trial comprised nine treatment groups: four groups have been

discontinued, and five have completed the trial (Fig. 1). Participants in the five groups for which results are reported here were enrolled across eight countries and regions (see the Supplementary Appendix, available at NEJM.org).

Participants were randomly assigned to one of four xalnesiran groups or the NA control group. Participants in group 1 received 100 mg of xalnesiran, those in group 2 received 200 mg of xalnesiran, those in group 3 received 200 mg of xalnesiran plus 150 mg of ruzotolimod, those in group 4 received 200 mg of xalnesiran plus 180 μg of peginterferon alfa-2a, and those in group 5 received NA therapy. Participants were in the trial for 96 weeks, which included a 48-week treatment period and a 48-week follow-up period. Xalnesiran was administered subcutaneously every 4 weeks for 48 weeks, ruzotolimod orally every other day from weeks 13 to 24 and from weeks 37 to 48, and peginterferon alfa-2a subcutaneously weekly for 48 weeks.

The established daily oral administration of NA therapy continued in the participants in all groups until the criteria for stopping NA therapy were met at the end of treatment or during the follow-up period. The criteria for stopping NA therapy were as follows: an ALT level of less than 1.25 times the baseline value, an HBV DNA level of less than 20 IU per milliliter, negative test results for hepatitis B e antigen (HBeAg), and HBsAg loss

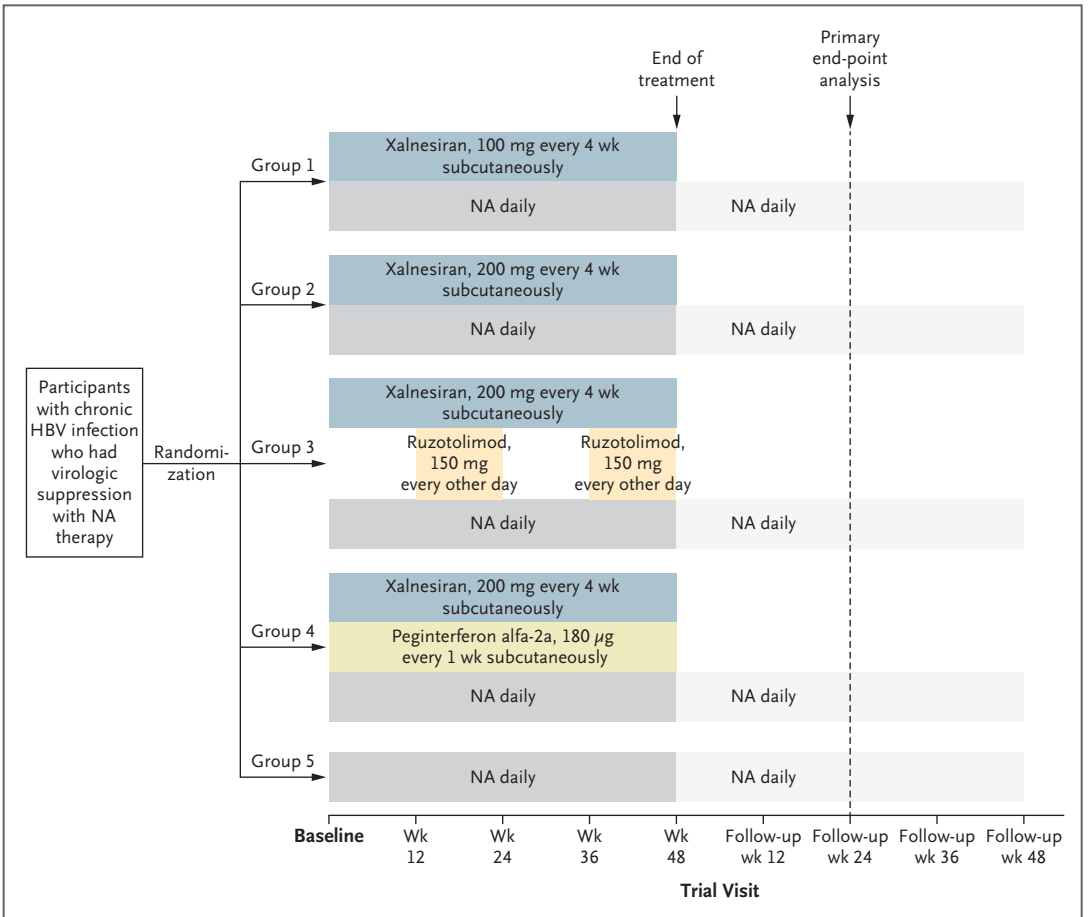

Figure 1. Trial Design.

The randomization ratio was dynamic, and randomization was conducted in a 1:1 ratio to the initial treatment groups, which were the early-terminated linvencorvir–ruzotolimod group (data not shown) and the first 31 participants of the group that received nucleoside or nucleotide analogue (NA) therapy (group 5) (see the Supplementary Methods section in the Supplementary Appendix). Subsequently, randomization was adapted depending on the number of enrolling treatment groups (with the stipulation that ≤17% of the participants would be randomly assigned to group 5). NA therapy continued until the stopping criteria were met at the end of treatment (week 48) or during the follow-up period.

(HBsAg level, <0.05 IU per milliliter) or an HBsAg level of less than 100 IU per milliliter with a decrease from baseline of at least 1 $\log_{10}$ IU per milliliter. The criteria for restarting NA therapy included an HBV DNA level above 20,000 IU per milliliter, an ALT level above 1.5 times the ULN and an HBV DNA level above 2000 IU per milliliter, an ALT level below 1.5 times the ULN and an HBV DNA level above 2000 IU per milliliter with a retest of the HBV DNA level within 1 week to confirm that the HBV DNA level was still above 2000 IU per milliliter, or clinically significant signs of decreasing liver function. (Current and previous versions of the criteria for stopping and restarting NA therapy are described in the Supplementary Methods section in the Supplementary Appendix.)

Randomization was dynamic and conducted in a 1:1 ratio for the initial treatment groups, which were the early-terminated linvencorvir–ruzotolimod group and the first 31 participants in group 5 (NA alone). Randomization was subsequently adapted depending on the number of enrolling treatment groups, with the stipulation that no more than 17% of the participants would be randomly assigned to the NA group. Randomization was conducted by means of an interactive Web-response system, with the use of an adaptive stratified sampling method with minimization. For the initial treatment groups, randomization was stratified according to the screening HBsAg level (<1000 vs. ≥1000 IU per milliliter), with a minimum of 12 participants per group with an HBsAg level below 1000 IU per milliliter. For subsequent groups, the proportion of participants with an HBsAg level below 1000 IU per milliliter was maintained as closely as possible to the proportion in the initial treatment groups.

END POINTS

The primary efficacy end point was HBsAg loss, defined as an HBsAg level below 0.05 IU per milliliter, at 24 weeks after the end of the 48-week treatment period. Secondary end points included HBsAg loss at time points different from that of the primary end point, HBsAg seroconversion, an HBV DNA level of less than 10 IU per milliliter (i.e., the lower limit of quantification of the assay), HBeAg loss and HBeAg seroconversion in participants who were HBeAg-positive at baseline, and the change from baseline in the HBsAg and HBeAg levels. Exploratory analyses evaluated outcomes in participants with a baseline HBsAg level below 1000 IU per milliliter, concomitant HBsAg loss, and an HBV DNA level of less than 10 IU per milliliter, and post hoc analyses included the evaluation of events and outcomes of the discontinuation of NA therapy, the change in HBsAg loss, and the durability of HBsAg loss during the follow-up period.

Safety was evaluated according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. The intention-to-treat population included all the participants who had undergone randomization. The modified intention-to-treat population included all the participants who had undergone randomization and received at least one dose of each drug from their assigned regimen. The safety population included all the participants who received at least one dose of any drug from their assigned regimen.

STATISTICAL ANALYSIS

The trial was designed to enroll approximately 30 participants per group. Assuming that 3% of the participants in the NA group (group 5) would have a response, we calculated that 30 participants per group would provide the trial with 78% power to detect an absolute 30-percentage-point pairwise difference between any xalnesiran group and the NA group, on the basis of a continuity-corrected, two-sided chi-square test of equal proportions for the two treatment groups at an alpha level of 5%.

For the primary end point, we estimated the treatment differences with adjustment for the HBsAg level at screening (stratification factor), along with the associated 95% confidence intervals, using the NA group as the reference. The confidence intervals were calculated by the Cochran–Mantel–Haenszel weighting method with continuity correction. Missing data at the time point for the primary analysis, including data for participants who discontinued before this time point, were considered to indicate nonresponse. The primary analysis was performed in the modified intention-to-treat population. No prespecified adjustment for multiple comparisons and no formal hypothesis testing were planned. The widths of the 95% confidence intervals were therefore not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Statistical analyses were conducted with the use of R software, version 4.0.4. Further information about the statistical methods is provided in the Supplementary Methods section.

RESULTS

PARTICIPANTS

Participants were enrolled in the trial between July 5, 2020, and November 29, 2021, and completed the trial between February 22, 2021, and October 2, 2023. The intention-to-treat population included 160 participants, with 124 participants assigned to a xalnesiran group (groups 1 through 4) and 36 to the NA group (group 5). The modified intention-to-treat population included 159 participants; 1 participant in group 5 who discontinued the trial before receiving trial treatment was excluded from this population. Overall, 7% of the participants discontinued the trial (10 participant withdrawals and 1 protocol deviation), and 3% discontinued during the treatment period (5 participant withdrawals) (Fig. S1 in the Supplementary Appendix).

The characteristics of the participants at baseline were generally well balanced across the trial groups (Table 1). Overall, 94% of the participants were Asian, and 70% were HBeAg-negative (with data on HBeAg status missing for one participant in group 5). The trial population, which included persons who had virologic suppression with NA therapy, was representative of the age of the general population of persons with chronic HBV infection but was not fully representative of the sex, racial, and geographic distribution of such persons (Table S1).

EFFICACY

The highest percentages of participants with HBsAg loss at 24 weeks after the end of treatment (the primary end point) were observed in the groups that received xalnesiran plus an immunomodulator: 12% (95% confidence interval [CI], 3 to 28) in group 3 and 23% (95% CI, 10 to 42) in group 4, as compared with 7% (95% CI, 1 to 22) in group 1, 3% (95% CI, 0 to 17) in group 2, and none (95% CI, 0 to 10) in group 5 (Table 2). The corresponding estimated differences for groups 1 through 4 as compared with group 5 were 7 percentage points (95% CI, −2 to 16), 4 percentage points (95% CI, −3 to 10), 12 percentage points (95% CI, 1 to 23), and 24 percentage points (95% CI, 9 to 40) (Table S2). The coronavirus disease 2019 pandemic had a minimal effect on the primary end-point results. Overall, 13 participants missed three or more consecutive doses of xalnesiran. A supplementary analysis of the primary end point in which events of three or more consecutive missed doses of xalnesiran were considered to be intercurrent (i.e., an event that occurred after the application of treatment and that either precluded observation of the variable or affected the interpretation of it) and were imputed did not show any appreciable difference from the analysis in the modified intention-to-treat population (Table S3).

The highest percentages of participants with HBsAg seroconversion were observed in group 4: 23% at the end of treatment, 20% at 24 weeks after the end of treatment, and 17% at 48 weeks after the end of treatment. The percentages of participants with HBsAg seroconversion in the other groups were 6% or less at these time points (Table 2).

HBsAg loss and seroconversion were observed only in participants who had an HBsAg level below 1000 IU per milliliter at screening. Among participants who had an HBsAg level below 1000 IU per milliliter at screening, HBsAg loss occurred in 47% and seroconversion in 40% of those in group 4 at 24 weeks after the end of treatment, as compared with 7 to 24% of the participants with HBsAg loss and no more than 7% of those with seroconversion in groups 1, 2, and 3 (Table 2).

The percentages of participants with HBsAg loss were generally highest at the end of treatment: 7%, 3%, 18%, 30%, and none in groups 1 through 5, respectively. In an analysis that used the percentage of participants with HBsAg loss at the end of treatment as a reference, the durability of HBsAg loss at 24 weeks after the end of treatment was 100%, 100%, 67%, and 78% in groups 1 through 4, respectively. The durability of HBsAg loss at 48 weeks after the end of treatment was 150% in group 1, 67% in group 3, and 56% in group 4, with no durability of HBsAg loss observed in group 2 at this time point (Table S4).

Substantial reductions in HBsAg levels were observed across groups 1 through 4. In particular, the percentages of participants in groups 1 through 4 with an HBsAg level below 100 IU per milliliter were 9 to 17% at baseline, 63 to 93% at the end of treatment, and 40 to 60% at 48 weeks after the end of treatment, as compared with 14%, 20%, and 26%, respectively, in group 5 (Fig. S2). The difference in the adjusted mean reduction in the HBsAg level between groups 1 through 4 and group 5 (reference) ranged from

Table 1. Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	Group 1: Xalnesiran, 100 mg (N=30)	Group 2: Xalnesiran, 200 mg (N=30)	Group 3: Xalnesiran, 200 mg + Ruzotolimod (N=34)	Group 4: Xalnesiran, 200 mg + Peginterferon Alfa-2a (N=30)	Group 5: NA Alone (N=36)
Age — yr	42.8±10.7	40.0±11.0	42.6±8.5	38.1±9.5	43.6±9.2
Male sex — no. (%)	29 (97)	20 (67)	30 (88)	25 (83)	28 (78)
Body-mass index†‡	24.7±3.6	23.6±3.0	24.7±2.8	23.0±2.1	23.8±2.9
Race or ethnic group — no. (%)§					
Asian	26 (87)	29 (97)	32 (94)	30 (100)	33 (92)
White	3 (10)	1 (3)	0	0	2 (6)
Black	0	0	2 (6)	0	0
Native Hawaiian or Pacific Islander	1 (3)	0	0	0	1 (3)
Screening HBsAg <1000 IU/ml — no. (%)¶	14 (47)	15 (50)	17 (50)	15 (50)	20 (56)
Baseline HBsAg — $\log_{10}$ IU/ml‡¶	2.8±0.8	2.8±1.0	2.9±1.0	2.9±0.8	2.8±1.0
HBeAg-positive status — no./total no. (%)‡	9/30 (30)	8/30 (27)	10/34 (29)	12/30 (40)	8/35 (23)
HBV DNA‡					
Mean — IU/ml‖	10.1±0.4	10.0±0.0	10.0±0.2	10.0±0.0	10.0±0.2
Distribution — no./total no. (%)					
<10 IU/ml	29/30 (97)	30/30 (100)	33/34 (97)	30/30 (100)	33/35 (94)
10 to <20 IU/ml	1/30 (3)	0/30	1/34 (3)	0/30	2/35 (6)
Alanine aminotransferase‡					
Mean — U/liter	20.4±9.3	17.7±8.2	21.6±7.5	20.8±7.1	24.0±10.1
Distribution — no./total no. (%)					
≤1 ×ULN	29/30 (97)	30/30 (100)	34/34 (100)	30/30 (100)	33/35 (94)
>1 to ≤1.5 ×ULN	1/30 (3)	0/30	0/34	0/30	2/35 (6)
Duration of previous NA treatment — yr**	6.2±3.8	6.1±4.0	7.4±4.7	8.6±5.0	8.5±6.5
Previous resistance to NA therapy — no. (%)	3 (10)	0	1 (3)	5 (17)	5 (14)
Median transient elastography (range) — kPa††	5.2 (3.3–7.0)	4.9 (2.6–7.0)	4.7 (2.9–7.3)	4.8 (3.1–7.2)	4.9 (2.9–7.3)

* Plus–minus values are means ±SD. The intention-to-treat population included all the participants who had undergone randomization. Percentages may not total 100 because of rounding. HBeAg denotes hepatitis B e antigen, HBsAg hepatitis B surface antigen, HBV hepatitis B virus, NA nucleoside or nucleotide analogue, and ULN upper limit of the normal range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ One participant in group 5 discontinued the trial before baseline, so some information about this participant was not available.

§ Race and ethnic group were reported by the participant.

¶ The screening visit was conducted 7 to 57 days before the start of the trial, and the value at screening was used to implement the stratified randomization (HBsAg threshold, 1000 IU per milliliter). The baseline visit happened on day 1 of the trial, and sampling for HBsAg quantification was conducted before treatment administration.

‖ To calculate the mean, HBV DNA values that had been reported as being below 10 IU per milliliter or as "target not detected" were imputed as 10 IU per milliliter.

** Data were missing for one participant who had been randomly assigned to group 2.

†† Transient elastographic data were reported for 29 participants in group 1, for 29 in group 2, for 34 in group 3, for 30 in group 4, and for 34 in group 5. Acoustic radiation force impulse elastographic data were reported for the four participants (one in group 1, one in group 2, and two in group 5) with no transient elastography report, all of whom had a value of 1.1 m per second.

Table 2. HBsAg and HBV DNA Treatment Response in the Modified Intention-to-Treat Population and According to Stratum with HBsAg Level below 1000 IU per Milliliter at Screening.*

End Point	Modified Intention-to-Treat Population					Participants with Screening HBsAg Level <1000 IU/ml				
	Group 1: Xalnesiran, 100 mg (N=30)	Group 2: Xalnesiran, 200 mg (N=30)	Group 3: Xalnesiran, 200 mg + Ruzotolimod (N=34)	Group 4: Xalnesiran, 200 mg + Peginterferon Alfa-2a (N=30)	Group 5: NA Alone (N=35)	Group 1: Xalnesiran, 100 mg (N=14)	Group 2: Xalnesiran, 200 mg (N=15)	Group 3: Xalnesiran, 200 mg + Ruzotolimod (N=17)	Group 4: Xalnesiran, 200 mg + Peginterferon Alfa-2a (N=15)	Group 5: NA Alone (N=19)
	number of participants (percent)									
HBsAg loss										
At the end of treatment	2 (7)	1 (3)†	6 (18)	9 (30)	0	2 (14)	1 (7)†	6 (35)	9 (60)	0
Primary end point: at 24 wk after the end of treatment	2 (7)	1 (3)†	4 (12)	7 (23)	0	2 (14)	1 (7)†	4 (24)	7 (47)	0
At 48 wk after the end of treatment	3 (10)‡	0	4 (12)	5 (17)	1 (3)	3 (21)‡	0	4 (24)	5 (33)	1 (5)
HBsAg seroconversion										
At the end of treatment	1 (3)	0	0	7 (23)	0	1 (7)	0	0	7 (47)	0
At 24 wk after the end of treatment	1 (3)	0	1 (3)	6 (20)	0	1 (7)	0	1 (6)	6 (40)	0
At 48 wk after the end of treatment	1 (3)	0	2 (6)	5 (17)	1 (3)	1 (7)	0	2 (12)	5 (33)	1 (5)
HBsAg loss and HBV DNA <10 IU/ml										
At the end of treatment	2 (7)	1 (3)†	6 (18)	9 (30)	0	2 (14)	1 (7)†	6 (35)	9 (60)	0
At 24 wk after the end of treatment	1 (3)	1 (3)†	3 (9)	7 (23)	0	1 (7)	1 (7)†	3 (18)	7 (47)	0
At 48 wk after the end of treatment	3 (10)‡	0	2 (6)	5 (17)	1 (3)	3 (21)‡	0	2 (12)	5 (33)	1 (5)

* HBsAg loss was defined as an HBsAg level below 0.05 IU per milliliter. The primary end point was HBsAg loss at 24 weeks after the end of treatment. The modified intention-to-treat population included all the participants who had undergone randomization and received at least one dose of each drug from their assigned regimen. All the participants continued their established NA regimen (entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate) until the criteria for stopping NA therapy were met at the end of treatment (week 48) or during the follow-up period. The analysis involving participants with an HBsAg level below 1000 IU per milliliter at screening was an exploratory analysis (see the statistical analysis plan, available with the protocol).

† In group 2, HBsAg loss was observed at baseline before the start of treatment with 200 mg of xalnesiran in one participant.

‡ In group 1, one participant had HBsAg loss after discontinuing NA therapy.

1.4 to 2.1 $\log_{10}$ IU per milliliter at the end of treatment and from 0.7 to 1.1 $\log_{10}$ IU per milliliter at 48 weeks after the end of treatment (Table S5).

The majority of participants had an HBV DNA level below 10 IU per milliliter throughout the trial (Table S6). HBsAg loss was consistently associated with HBV DNA levels below 10 IU per milliliter, except in three participants (Table 2).

Among the 39 participants across groups 1 through 4 who were HBeAg-positive at baseline, HBeAg loss was observed in 51% at the end of treatment, in 33% at 24 weeks after the end of treatment, and in 36% at 48 weeks after the end of treatment; HBeAg seroconversion was observed in 13% at the end of treatment, in 10% at 24 weeks after the end of treatment, and in 21% at 48 weeks after the end of treatment (Table S7). The unadjusted mean HBsAg levels and changes from baseline are shown in Figures S3 through S6, and the unadjusted mean HBeAg levels and changes from baseline are shown in Figures S7 and S8.

STOPPING AND RESTARTING OF NA THERAPY

Across the 124 participants in groups 1 through 4, a total of 58 participants (47%) met the criteria for stopping NA therapy and 40 (32%) stopped NA therapy. Among the 40 participants who stopped, virologic relapse (defined as an HBV DNA level >2000 IU per milliliter) was observed in 19 (48%) and clinical relapse (defined as an HBV DNA level >2000 IU per milliliter and an ALT level >2 times the ULN) was observed in 3 (8%). NA therapy was subsequently restarted in 16 of the 40 participants (40%). A total of 24 of 40 participants (60%) were not receiving NA therapy at 48 weeks after the end of treatment; 11 participants (28%) had a quantifiable HBsAg level and a quantifiable HBV DNA level below 2000 IU per milliliter, 6 (15%) had a quantifiable HBsAg level and an HBV DNA below 10 IU per milliliter, 2 (5%) had HBsAg loss and a quantifiable HBV DNA level below 2000 IU per milliliter, and 5 (12%) had HBsAg loss and an HBV DNA level below 10 IU per milliliter (Table S8).

CHANGES IN ALT LEVELS

Overall, 54% of the participants had an elevated ALT level during the treatment period or during follow-up, including 6% with an event classified as grade 3 or 4 (Table S9). All elevations in the ALT level were associated with preserved liver synthetic and excretory functions, were not associated with an increased bilirubin level, and resolved without sequelae. Among all the participants who had an elevated ALT level, one in group 3 had a transient increase in the international normalized ratio (grade 2 elevation in the ALT level [4.5 times the ULN] and an increased international normalized ratio to 2.2 times the ULN). The international normalized ratio in this participant returned to below 1.0 times the ULN within 1 week, and the bilirubin level remained within the normal range, with no signs or symptoms suggesting liver decompensation. One grade 4 elevation in the ALT level was observed in group 3 (maximum HBV DNA level, 1,400,000 IU per milliliter; maximum ALT level, 23 times the ULN; maximum total bilirubin level, 1.1 times the ULN) during the follow-up period in the context of a clinical relapse after the discontinuation of NA therapy, which subsequently resolved after NA therapy was restarted.

ADVERSE EVENTS

Overall, 159 participants were included in the safety population. Adverse events were reported in 97% or more of the participants in groups 1 through 4 and in 77% of the participants in group 5 (Table 3). Common adverse events in groups 1 through 4 included an increased ALT level (in 43 to 83% of the participants), an increased aspartate aminotransferase level (in 20 to 70%), upper respiratory tract infection (in 12 to 47%), and injection-site reaction (in 7 to 50%). Influenza-like illness occurred in 47% of the participants in group 3 and in 27% of those in group 4. No instances of injection-site reaction or influenza-like illness were considered by the investigators to be serious. Adverse events of elevated liver-enzyme levels and cytopenias were most frequent in participants treated with peginterferon alfa-2a (group 4).

An adverse event of grade 3 or 4 occurred in 17% of the participants in group 1, in 10% of those in group 2, in 18% of those in group 3, in 50% of those in group 4, and in 6% of those in group 5 (Table 3). The most frequent adverse event of grade 3 or 4 was an elevated ALT level, which occurred in 13% of the participants in group 4 (all events of grade 3) and in 3% or less of the participants in the other groups (Table S10). Across groups 1 through 5, serious adverse events occurred in 10%, 13%, 6%, 7%, and 3% of the participants, respectively

Table 3. Safety Analysis (Safety Population).*

Event	Group 1: Xalnesiran, 100 mg (N=30)	Group 2: Xalnesiran, 200 mg (N=30)	Group 3: Xalnesiran, 200 mg + Ruzotolimod (N=34)	Group 4: Xalnesiran, 200 mg + Peginterferon Alfa-2a (N=30)	Group 5: NA Alone (N=35)
			number of participants (percent)		
Any adverse event	30 (100)	29 (97)	33 (97)	30 (100)	27 (77)
Adverse event related to treatment	22 (73)	19 (63)	26 (76)	30 (100)	4 (11)
Grade 3 or 4 adverse event	5 (17)	3 (10)	6 (18)	15 (50)	2 (6)
Grade 5 adverse event	0	0	0	0	0
Serious adverse event	3 (10)	4 (13)	2 (6)	2 (7)	1 (3)
Serious adverse event related to treatment	0	0	0	1 (3)	0
Adverse event leading to withdrawal from treatment	1 (3)	0	2 (6)	6 (20)	1 (3)
Adverse event leading to withdrawal from treatment related to treatment	1 (3)	0	2 (6)	5 (17)	1 (3)
Adverse event leading to dose modification or interruption	1 (3)	0	5 (15)	12 (40)	0
Adverse event leading to dose modification or interruption related to treatment	0	0	5 (15)	12 (40)	0
Adverse event leading to trial withdrawal	0	0	0	0	0
Adverse event occurring in ≥10% of participants overall					
ALT increased	13 (43)	13 (43)	15 (44)	25 (83)	3 (9)
Covid-19	10 (33)	16 (53)	17 (50)	17 (57)	8 (23)
AST increased	6 (20)	10 (33)	11 (32)	21 (70)	1 (3)
Upper respiratory tract infection	14 (47)	11 (37)	4 (12)	13 (43)	4 (11)
Injection-site reaction	2 (7)	9 (30)	7 (21)	15 (50)	1 (3)
Influenza-like illness	0	0	16 (47)	8 (27)	0
Amylase increased	5 (17)	5 (17)	5 (15)	6 (20)	1 (3)
HBV reactivation	6 (20)	1 (3)	10 (29)	2 (7)	3 (9)
Neutrophil count decreased	1 (3)	1 (3)	6 (18)	12 (40)	1 (3)
Platelet count decreased	0	0	3 (9)	17 (57)	1 (3)
Hepatic steatosis	7 (23)	3 (10)	2 (6)	6 (20)	4 (11)
Hyperlipidemia	6 (20)	7 (23)	4 (12)	1 (3)	1 (3)
Hyperuricemia	6 (20)	6 (20)	2 (6)	3 (10)	1 (3)
Pyrexia	0	3 (10)	7 (21)	7 (23)	1 (3)
White-cell count decreased	1 (3)	1 (3)	5 (15)	8 (27)	1 (3)

* The safety population included all the participants who received at least one dose of any drug from their assigned regimen. Participants may have had more than one adverse event in the category listed. Investigator text for adverse events were encoded with the use of the *Medical Dictionary for Regulatory Activities*, version 26.1, and are presented according to preferred terms. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and Covid-19 coronavirus disease 2019.

(multiple events may have occurred in the same participant) (Table 3 and Table S11). The only treatment-related serious adverse event occurred in group 4, which was a panic attack that was deemed by the investigator to be related to peginterferon alfa-2a therapy. No fatal adverse events occurred during the trial.

Adverse events leading to withdrawal from treatment or to dose modification or interruption occurred most frequently in group 4 (Table 3). No adverse events led to withdrawal from the trial.

DISCUSSION

The Piranga trial showed that 48 weeks of therapy with xalnesiran plus an immunomodulator resulted in substantial percentages of participants with HBsAg loss. The percentage of patients with HBsAg loss that was observed with xalnesiran plus peginterferon alfa-2a, 23% at 24 weeks after the end of treatment, was higher than the percentages that have been reported for current standard-care approaches[9-11,18,19] and the majority of new oligonucleotide-based regimens, although differing trial populations limit cross-trial comparisons.[20-26] With xalnesiran and peginterferon alfa-2a therapy, HBsAg loss with seroconversion occurred in 20% of the participants at 24 weeks after the end of treatment. Despite the convenient oral route of administration of ruzotolimod, the percentage of patients with HBsAg loss or seroconversion appeared to be lower with xalnesiran plus ruzotolimod than with xalnesiran plus peginterferon alfa-2a.

HBsAg loss with or without seroconversion was observed only in participants who had an HBsAg level below 1000 IU per milliliter at screening, including 60% of the participants who had HBsAg loss at the end of treatment with xalnesiran plus peginterferon alfa-2a. These results are consistent with the hypothesis that a low pretreatment HBsAg level is prognostic for HBsAg loss,[20,27] a situation that highlights the challenge of obtaining a functional cure in patients with high HBsAg. Despite the high percentages of participants with HBsAg loss that were observed in the immunomodulatory-therapy groups at the end of treatment, erosion of this response was observed during the follow-up period — a situation that was similar to that seen with other investigational oligonucleotide regimens.[20,24-26] Most erosion of HBsAg loss occurred soon after the end of treatment; however, some erosion was observed at later time points. In group 4, the durability of HBsAg loss decreased from 78% to 56% between 24 weeks and 48 weeks after the end of treatment, which underscores the need for a sufficiently long duration of follow-up to assess the durability of HBsAg loss induced by new agents.

Xalnesiran with or without an immunomodulator resulted in substantial reduction in the HBsAg level during treatment, with up to 60% of the participants having an HBsAg level maintained below 100 IU per milliliter at 48 weeks after the end of treatment. This finding is consistent with results of a previous study[15] and with the long half-life of *N*-acetyl-D-galactosamine–conjugated small interfering RNA molecules in the liver.[28,29] However, the addition of an immunomodulator was essential for HBsAg loss.

The withdrawal of NA treatment is a requirement for finite-duration functional-cure therapies but is associated with risks.[30] Our trial showed that the stopping of NA therapy can be safely managed with prespecified stopping and restarting criteria and with rigorous safety monitoring.[31]

In this trial, treatment with xalnesiran with or without an immunomodulator for 48 weeks had a safety profile that was consistent with the safety profiles of the individual drugs.[15,32-34] An elevated ALT level was the most common adverse event across the xalnesiran groups and was most frequently observed in combination with peginterferon alfa-2a. All these events were asymptomatic, were considered by the investigator to be nonserious, and resolved without evidence of liver dysfunction. Influenza-like illness and pyrexia were associated predominantly with ruzotolimod; these events are related to TLR7 activation and are biologic markers of on-target pharmacodynamic effect.[35]

Strengths of this trial include an adaptive trial design, the use of a common control group as the comparator, and the stratification of participants according to the HBsAg level at screening. Limitations include the inability of the trial to compare outcomes formally among the investigational treatment groups since the trial did not include groups with ruzotolimod or peginterferon alfa-2a alone and was designed to use the group that received NA therapy alone as the common comparator (control). Additional limitations include the small per-group sample size, the overrepresentation of male participants and

participants of Asian race, and the exclusion of participants who had not received NA therapy previously or who had clinically significant fibrosis. Finally, the absence of longitudinal immunologic and intrahepatic assessments limited the understanding of the relation between treatment outcomes and the underlying immunopathophysiological characteristics of the disease.

This phase 2 trial showed that treatment with xalnesiran plus an immunomodulator led to substantial percentages of participants with HBsAg loss, while identifying challenges in durability of HBsAg loss and efficacy in participants with high HBsAg levels. To address these challenges, a potential approach could be to specifically target adaptive immunity and restore HBV-specific exhausted T cells. Combination regimens containing checkpoint inhibitors are being explored in chronic hepatitis B,[36,37] including a liver-targeted locked nucleic acid that degrades programmed death ligand 1 expression[38] and is being evaluated in combination with xalnesiran in other groups of the Piranga platform trial.

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APPENDIX

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