

ORIGINAL ARTICLE

A Phase 2 Trial of Tobevibart plus Elebsiran in Hepatitis D

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ABSTRACT

BACKGROUND

Both tobevibart (a monoclonal antibody) and elebsiran (a small interfering RNA) target hepatitis B virus surface antigen (HBsAg). Their efficacy and safety in the treatment of chronic hepatitis D virus (HDV) infection are unknown.

METHODS

In this ongoing, phase 2, open-label trial, we randomly assigned participants to receive tobevibart plus elebsiran every 4 weeks or tobevibart monotherapy every 2 weeks. The primary end point was a combined response, defined by an HDV RNA level below the limit of detection or a decrease in the HDV RNA level of at least 2 log₁₀ IU per milliliter from baseline (virologic response) and normalization of the alanine aminotransferase (ALT) level, at week 24.

RESULTS

At week 24, a combined response was observed in 47% of participants (15 of 32) who received tobevibart plus elebsiran and in 70% of participants (23 of 33) who received tobevibart, with a virologic response in 100% (32 of 32) and 82% (27 of 33), respectively, and normalization of the ALT level in 47% (15 of 32) and 76% (25 of 33). At week 48, a combined response was observed in 56% of participants (18 of 32) with tobevibart plus elebsiran and 61% of participants (20 of 33) with tobevibart; undetectable HDV RNA (also known as target not detected, or TND; no amplification during reverse-transcriptase–polymerase-chain-reaction assay) in 66% (21 of 32) and 48% (16 of 33), respectively; normalization of the ALT level in 56% (18 of 32) and 61% (20 of 33); and an HBsAg level below 10 IU per milliliter in 91% (29 of 32) and 21% (7 of 33). No ALT flares were observed in participants starting tobevibart and elebsiran simultaneously or receiving tobevibart monotherapy. Through week 48, a total of 81% of participants who received tobevibart plus elebsiran and 94% of those who received tobevibart had at least one adverse event, primarily influenza-like illness and chills.

CONCLUSIONS

In this phase 2 trial, tobevibart plus elebsiran as well as tobevibart monotherapy decreased HDV RNA and ALT levels through week 48. Treatment with tobevibart plus elebsiran was associated with a high incidence of undetectable HDV RNA and of a decrease in the HBsAg level. (Funded by Vir Biotechnology; ClinicalTrials.gov number, NCT05461170.)

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This article was published on November 9, 2025, at NEJM.org.

DOI: [10.1056/NEJMoa2508827](https://doi.org/10.1056/NEJMoa2508827)

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HEPATITIS D VIRUS (HDV), ALSO KNOWN as hepatitis delta virus, is a satellite RNA virus that requires hepatitis B virus (HBV) surface antigen (HBsAg) for entry and propagation within hepatocytes.^{1,2} Globally, HDV infection affects approximately 12 million persons.²⁻⁴ Chronic HDV infection, the most severe form of chronic viral hepatitis,^{1,5} is associated with increased risks of cirrhosis, hepatocellular carcinoma, and death and has limited treatment options.⁶⁻⁹

Bulevirtide, an entry inhibitor that reduces viral spreading, is available in some regions and is the only agent approved by the European Medicines Agency for long-term treatment of HDV.¹⁰ Finite therapy with pegylated interferon (peginterferon) alfa is recommended in the European Association for the Study of the Liver guidelines; however, it has limited efficacy and is contraindicated in many patients owing to side effects.^{2,11} In the MYR 301 trial, 12% of participants who received bulevirtide at a dose of 2 mg per day had undetectable HDV RNA (also known as target not detected, or TND; no amplification during reverse-transcriptase–polymerase-chain-reaction [RT-PCR] assay) at week 48 despite either an undetectable HDV RNA level or a decrease in the HDV RNA level of at least 2 log₁₀ IU per milliliter in 71% of participants.¹² In addition, bulevirtide requires daily subcutaneous injections, has minimal effect on HBsAg, and is associated with a high risk of relapse after the end of treatment.¹²⁻¹⁶

Studies of bulevirtide led to an improved understanding of the on-treatment responses associated with long-term control of HDV infection. Findings from these studies suggest that the most relevant goal of therapy is complete viral suppression, as indicated by undetectable HDV RNA.^{12,15,17}

Tobevibart and elebsiran have complementary mechanisms of action. Tobevibart is a broadly neutralizing anti-HBsAg monoclonal antibody that neutralizes HBV and HDV and blocks viral entry into hepatocytes.^{18,19} Elebsiran is a small interfering RNA (siRNA) that targets HBV messenger RNA and reduces HBsAg production.^{20,21} The ongoing phase 2 SOLSTICE trial is evaluating the efficacy and safety of tobevibart alone or combined with elebsiran for up to 192 weeks in participants with chronic HDV infection. Here, we report results through week 48, a key time point for evaluating HDV therapies.

METHODS

PARTICIPANTS

Eligible participants were 18 to younger than 70 years of age, had received a diagnosis of chronic HDV infection at least 6 months before screening and had an HDV RNA level of at least 500 IU per milliliter, had received nucleoside or nucleotide analogue therapy for at least the previous 12 weeks (and continued to receive such therapy throughout the trial), and had a serum alanine aminotransferase (ALT) level greater than the upper limit of the normal range but less than 5 times greater at screening. Key exclusion criteria were past or present decompensated cirrhosis (Child–Turcotte–Pugh class B or C), an ALT or aspartate aminotransferase level at least 5 times the upper limit of the normal range, and active infections besides HBV and HDV. Participants without cirrhosis had liver stiffness of less than 12 kPa (as measured by FibroScan [Echosens]) or a liver biopsy showing no cirrhosis (Metavir stage F0 through F3) within 12 months before screening and a platelet count of more than 150,000 cells per cubic millimeter. Participants with cirrhosis (Child–Turcotte–Pugh class A) had liver stiffness of at least 12 kPa or a liver biopsy showing cirrhosis (Metavir stage F4) within 12 months before screening and a platelet count of more than 90,000 cells per cubic millimeter. Full eligibility criteria are provided in the protocol, available with the full text of this article at NEJM.org.

TRIAL DESIGN

This ongoing, multicenter, randomized, open-label, three-part trial is being conducted at 20 sites across Bulgaria, France, Germany, Italy, Moldova, the Netherlands, New Zealand, Romania, and the United Kingdom. The trial includes a 6-week screening period and a treatment period of up to 192 weeks (Fig. 1).

Cohorts in parts 1 and 2 are described in the Methods section in the Supplementary Appendix, available at NEJM.org. This report focuses primarily on part 3, in which participants receiving nucleoside or nucleotide analogue therapy were randomly assigned in a 1:1 ratio through interactive response technology to receive tobevibart at dose of 300 mg subcutaneously plus elebsiran at a dose of 200 mg subcutaneously

every 4 weeks (cohort 2c) or tobevibart at a dose of 300 mg subcutaneously every 2 weeks (cohort 3). According to the protocol, part 3 aimed to include approximately 50% participants with cirrhosis; randomization was not stratified according to cirrhosis status. Participants in cohort 3 who did not have a decrease in the HDV RNA level of at least 1 log₁₀ IU per milliliter at week 24 or an HDV RNA level below the lower limit of quantification or a combined response (described below) at week 48 could transition to tobevibart plus elebsiran every 4 weeks (cohort 2c rollover). Cohort 2c rollover is ongoing; the cohort comprises participants receiving tobevibart plus elebsiran who transitioned from any monotherapy cohort. Tobeivibart and elebsiran were administered as separate subcutaneous injections by providers on the same day in different places on the body. Further details on each cohort are provided in the protocol.

TRIAL OVERSIGHT

The trial was conducted according to the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable local regulations. The protocol was approved by the institutional review board or independent ethics committee (or both) at each trial site. All the participants provided written informed consent. The trial was sponsored by Vir Biotechnology. All the authors had access to the trial data and contributed to the interpretation of data and drafting of the manuscript, with the assistance of professional medical writers who were funded by Vir Biotechnology. All the authors approved the final version of the submitted manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Confidentiality agreements were established between the authors and the sponsor.

ASSESSMENTS

To quantify serum HDV RNA, the RoboGene HDV DNA quantification kit, version 2.0 (Roboscreen Diagnostics), was used on the Roche LightCycler 480 Instrument II after manual RNA extraction with the INSTANT Virus RNA/DNA Kit (Analytik Jena) on a 400- μ l sample. The RoboGene assay has a limit of detection of 14 IU per milliliter and a lower limit of quantification

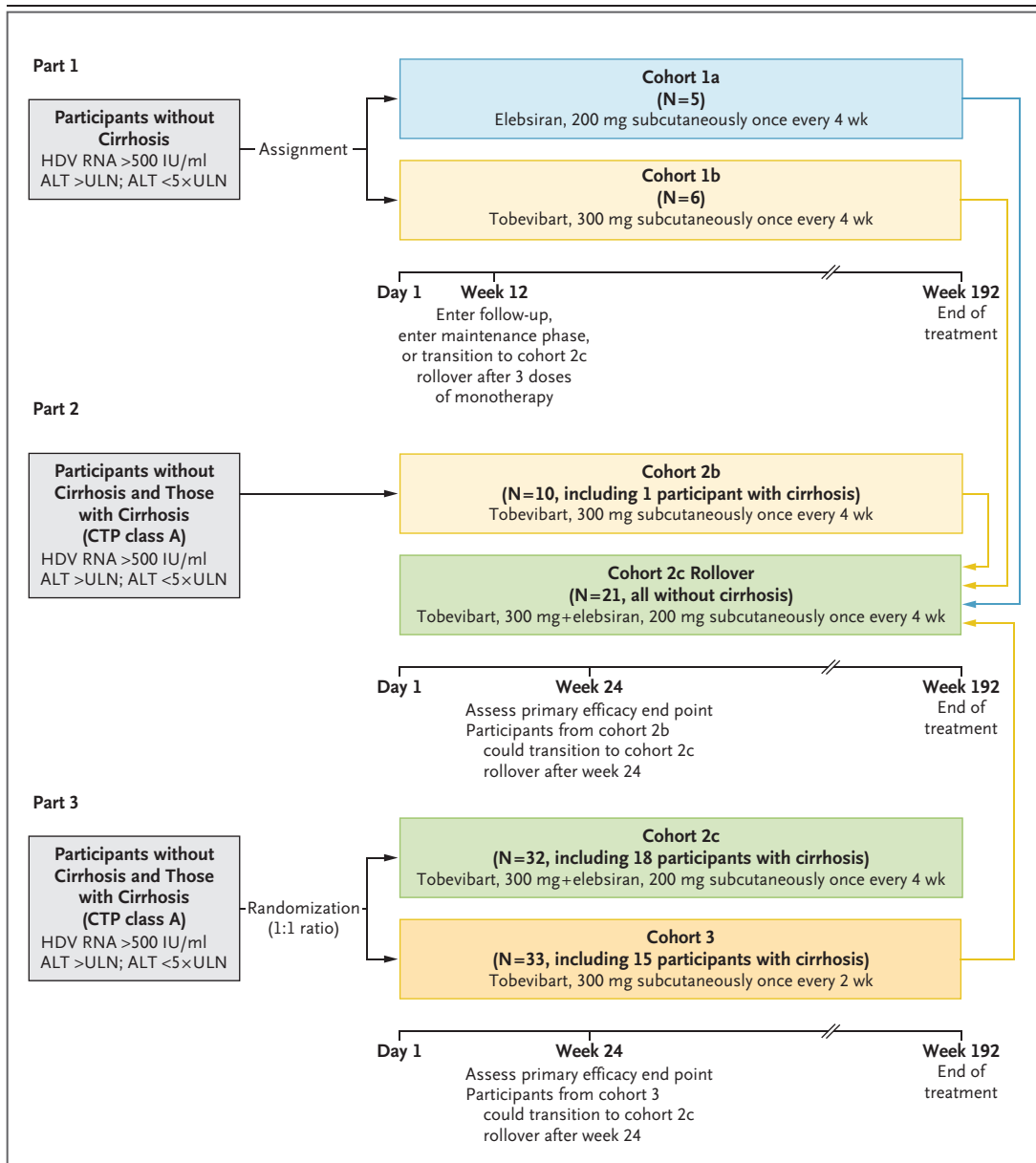
of 63 IU per milliliter. An HDV RNA level below the limit of detection or below the lower limit of quantification includes all values below the threshold and undetectable HDV RNA (target not detected, or TND; no amplification during RT-PCR assay). Normalization of the ALT level was defined as an ALT level below the upper limit of the normal range (40 IU per milliliter in men and 33 IU per milliliter in women). HBsAg was measured with the use of the Roche Elecsys HBsAg II assay, with a lower limit of quantification of 0.05 IU per milliliter. Safety assessments included documentation of adverse events (those that emerged or worsened on or after the date of the start of the trial drug up to 30 days after permanent discontinuation of the trial drug), serious adverse events, and clinical laboratory measurements.

END POINTS

The primary efficacy end point was a combined response, defined by an HDV RNA level below the limit of detection or a decrease in the HDV RNA level of at least 2 log₁₀ IU per milliliter from baseline (virologic response) and normalization of the ALT level, at week 24 in cohort 2c (excluding cohort 2c rollover) and cohort 3. The primary safety end point was the evaluation of adverse events and serious adverse events. Secondary end points included a combined response at weeks 12 and 48 and a virologic response, an HDV RNA level below the limit of detection, an HDV RNA level below the lower limit of quantification, undetectable HDV RNA, and normalization of the ALT level at weeks 12, 24, and 48. Undetectable HDV RNA is highlighted as a key virologic end point in regulatory guidance.²² The change from baseline in the HBsAg level was an exploratory end point. Table S1 in the Supplementary Appendix lists all prespecified end points.

STATISTICAL ANALYSIS

This trial had no prespecified statistical hypothesis testing or formal sample-size calculation. Efficacy and safety were analyzed in all participants who received any trial intervention. Efficacy data are reported with descriptive statistics for continuous variables (means and standard deviations) and as frequency counts with percentages and Clopper–Pearson 95% confidence intervals for categorical variables. Missing data were not imputed, except for efficacy responses with the use of the



“missing equals failure” approach. The widths of the confidence intervals were not adjusted for multiplicity and cannot be used for hypothesis testing. Safety analyses are summarized descriptively. Further details are available in the statistical analysis plan, available with the protocol.

RESULTS

PARTICIPANTS

Between August 23, 2022, and March 26, 2025, a total of 151 persons were screened and 95 were enrolled. A total of 32 participants were ran-

domly assigned to receive tobevibart plus elebsiran every 4 weeks and 35 to receive tobevibart every 2 weeks (2 participants withdrew consent before treatment). An additional 28 participants were enrolled across the monotherapy cohorts, and overall, 21 participants transitioned from a monotherapy cohort to tobevibart plus elebsiran every 4 weeks (see the Results section in the Supplementary Appendix and Fig. S1).

Approximately half the participants were men (52%), 82% were White, and 51% had cirrhosis (Table 1). The demographic and clinical characteristics of the monotherapy cohorts are report-

Figure 1 (facing page). Overview of Trial Design.

The SOLSTICE trial was conducted in three parts. In **part 1** (cohorts 1a and 1b), participants without cirrhosis (those with liver stiffness of <12 kPa or a liver biopsy showing no cirrhosis [Metavir stage F0 through F3] within 12 months before screening and a platelet count of >150,000 cells per cubic millimeter) were assigned to receive either elebsiran at a dose of 200 mg subcutaneously (cohort 1a) or tobevibart at a dose of 300 mg subcutaneously every 4 weeks (cohort 1b) up to week 12. Participants who did not have a combined response (hepatitis D virus [HDV] RNA level below the limit of detection or a decrease in the HDV RNA level of $\geq 2 \log_{10}$ IU per milliliter [virologic response] and normalization of the alanine aminotransferase [ALT] level) at week 12 could transition to tobevibart plus elebsiran (cohort 2c rollover) or enter follow-up. Participants who had a combined response at week 12 could enter a maintenance phase in which the dose of tobevibart or elebsiran monotherapy was reduced to every 8 weeks. In **part 2**, participants without cirrhosis received tobevibart at a dose of 300 mg subcutaneously every 4 weeks (cohort 2b) for up to 192 weeks. Participants without a decrease in the HDV RNA level of at least $1 \log_{10}$ IU per milliliter at week 24 could transition to tobevibart plus elebsiran (cohort 2c rollover). Cohort 2c rollover is ongoing; the cohort comprises participants receiving tobevibart plus elebsiran who transitioned from any monotherapy cohort. The figure reflects cohort 2c rollover at the week 48 time point of part 3. In **part 3**, participants were randomly assigned in a 1:1 ratio to receive either tobevibart (300 mg) plus elebsiran (200 mg) subcutaneously every 4 weeks (cohort 2c) or tobevibart (300 mg) subcutaneously every 2 weeks (cohort 3). Participants from cohort 3 who did not have a decrease in the HDV RNA level of at least $1 \log_{10}$ IU per milliliter at week 24 could transition to tobevibart plus elebsiran every 4 weeks (cohort 2c rollover). These cohorts included both participants without cirrhosis and those with compensated cirrhosis (Child–Turcotte–Pugh [CTP] class A; liver stiffness of ≥ 12 kPa or a liver biopsy showing cirrhosis [Metavir stage F4] within 12 months before screening and a platelet count of >90,000 cells per cubic millimeter). The primary end point was a combined response at week 24. The trial includes an interventional treatment period of up to 192 weeks. Participant replacement was allowed according to the protocol to ensure an adequate sample size for descriptive analysis. Part 3 also includes cohort 5, which includes participants without cirrhosis with a baseline hepatitis B virus surface antigen level of less than 10,000 IU per milliliter and liver stiffness of less than 8 kPa. Participants in this cohort received elebsiran at a dose of 200 mg every 4 weeks up to week 12 and then transitioned to cohort 2c rollover. At the time of this report, not all participants in cohort 5 had completed the three planned doses of elebsiran. ULN denotes upper limit of the normal range.

ed in Table S2. The representativeness of the trial population is described in Table S3.

PRIMARY END POINT

A combined response (virologic response and normalization of the ALT level) at week 24 (primary end point) was observed in 47% of participants (15 of 32) who received tobevibart plus elebsiran and in 70% of participants (23 of 33) who received tobevibart. At week 48, the percentages were 56% (18 of 32) and 61% (20 of 33), respectively (Table 2). Within each cohort, responses were generally similar in participants with cirrhosis and those without cirrhosis.

HDV RNA RESPONSES

Decreases in HDV RNA levels were observed over time in both cohorts (Figs. S2A and S3A). At week 24, a virologic response was observed in 100% of participants (32 of 32) who received tobevibart plus elebsiran and in 82% of participants (27 of 33) who received tobevibart; at week 48, the percentages were 97% (31 of 32) and 79% (26 of 33), respectively (Table 2). The percentages of participants who had an HDV RNA level below the limit of detection (<14 IU per milliliter) at week 48 were 88% (28 of 32 participants) with tobevibart plus elebsiran and 64% (21 of 33 participants) with tobevibart. For an HDV RNA level below the lower limit of quantification (<63 IU per milliliter), the percentages were 94% (30 of 32 participants) and 67% (22 of 33 participants), respectively (Table S4).

Undetectable HDV RNA (no amplification during RT-PCR assay) at week 24 was observed in 41% of participants (13 of 32) who received tobevibart plus elebsiran and in 30% of participants (10 of 33) who received tobevibart; at week 48, the percentages were 66% (21 of 32) and 48% (16 of 33), respectively (Table 2 and Fig. 2A). The percentages of participants with cirrhosis who had undetectable HDV RNA at week 24 were 50% (9 of 18 participants) with tobevibart plus elebsiran and 27% (4 of 15 participants) with tobevibart; at week 48, the percentages were 72% (13 of 18) and 40% (6 of 15), respectively.

NORMALIZATION OF ALT LEVEL

At week 24, normalization of the ALT level occurred in 47% of participants (15 of 32) who received tobevibart plus elebsiran and in 76% of participants (25 of 33) who received tobevibart

Table 1. Demographic and Clinical Characteristics of the Participants at Day 1.*

Characteristic	Tobevibart plus Elebsiran Every 4 Wk (N=32)	Tobevibart Every 2 Wk (N=33)
Age — yr	42±8	45±9
Male sex — no. (%)	18 (56)	16 (48)
Race — no. (%)†		
White	25 (78)	28 (85)
Asian	2 (6)	1 (3)
Black	4 (12)	2 (6)
Other	1 (3)	2 (6)
Body-mass index‡		
Mean	27±4	26±4
<30 — no. (%)	26 (81)	26 (79)
Cirrhosis — no. (%)§	18 (56)	15 (45)
Liver stiffness — kPa	13.5±7.3	13.5±8.7
Serum HDV RNA level — log ₁₀ IU/ml	5.7±1.2	5.6±1.1
HDV genotype — no. (%)¶		
1	31 (97)	32 (97)
5	1 (3)	1 (3)
HBeAg not detected — no. (%)	29 (91)	25 (76)
Serum HBsAg level — log ₁₀ IU/ml	3.7±0.6	3.7±0.8
Serum HBV DNA level — log ₁₀ IU/ml	0.7±0.7	0.7±0.8
ALT level — U/liter	83±47	76±59
Concomitant NA therapy — no. (%)	32 (100)	33 (100)
Tenofovir disoproxil fumarate	10 (31)	9 (27)
Tenofovir disoproxil	11 (34)	12 (36)
Entecavir	11 (34)	13 (39)
Previously exposed to agent with HDV activity — no. (%)	17 (53)	18 (55)
Interferon alfa	16 (50)	14 (42)
Bulevirtide	4 (12)	6 (18)
Lonafarnib	2 (6)	3 (9)
Other	2 (6)	1 (3)

* Plus-minus values are means ±SD. Participants were randomly assigned to receive either tobevibart plus elebsiran every 4 weeks (cohort 2c) or tobevibart every 2 weeks (cohort 3). Percentages may not total 100 because of rounding. ALT denotes alanine aminotransferase, HBV hepatitis B virus, HDV hepatitis D virus, HBeAg hepatitis B virus e antigen, HBsAg hepatitis B virus surface antigen, and NA nucleoside or nucleotide analogue.

† Race was reported by the participant. If a participant is reported to have multiple races, the participant is counted for each race reported.

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

§ Participants with cirrhosis (Child–Turcotte–Pugh class A) had a liver stiffness of at least 12 kPa or a liver biopsy showing cirrhosis (Metavir stage F4) within 12 months before screening and a platelet count of more than 90,000 cells per cubic millimeter.

¶ HDV genotype was determined by phylogenetic analysis of HDV genome sequencing from participants' baseline samples.

(Table 2 and Fig. 2B). At week 48, the percentages were 56% (18 of 32) and 61% (20 of 33), respectively. Normalization of the ALT level was generally similar in participants with cirrhosis and those without cirrhosis within each cohort (Table 2). Liver function appeared to be stable during the trial (Table S5).

HBSAG RESPONSE

The mean (±SD) change in serum HBsAg level at weeks 24 and 48 was -3.47 ± 0.44 and -3.56 ± 0.49 log₁₀ IU per milliliter, respectively, with tobevibart plus elebsiran and -1.79 ± 0.79 and -1.82 ± 0.76 log₁₀ IU per milliliter with tobevibart (Figs. S2C and S3C). The percentages of participants who had an HBsAg level below 10 IU per milliliter with tobevibart plus elebsiran were 88% (28 of 32 participants) at week 24 and 91% (29 of 32 participants) at week 48; the percentages with tobevibart were 21% (7 of 33 participants) at both weeks 24 and 48. In most participants, HBV DNA and hepatitis B virus e antigen levels below the limit of detection were sustained throughout the trial (Table S6).

SUBGROUP ANALYSIS AND MONOTHERAPY COHORTS

In both cohorts, the percentage of participants with undetectable HDV RNA appeared to be higher at weeks 24 and 48 in the subgroup of participants with a baseline HDV RNA level of less than 10⁵ IU per milliliter than in the subgroup with a baseline level of at least 10⁵ IU per milliliter (Table S7). Efficacy and safety data for the monotherapy cohorts are reported in the Results section in the Supplementary Appendix and Tables S8, S9, and S10.

SAFETY FINDINGS

Through week 48, a total of 81% of participants who received tobevibart plus elebsiran and 94% of those who received tobevibart had at least one adverse event. Most adverse events were mild or moderate in severity (Table 3 and Tables S9 and S10). The most common adverse events were influenza-like illness and chills, which typically occurred on day 1 after the first dose and resolved spontaneously within 24 to 48 hours. Injection-site reactions and adverse events that led to discontinuation of the trial drug were infrequent. One participant who received tobevibart had a serious adverse event involving hepatocellular car-

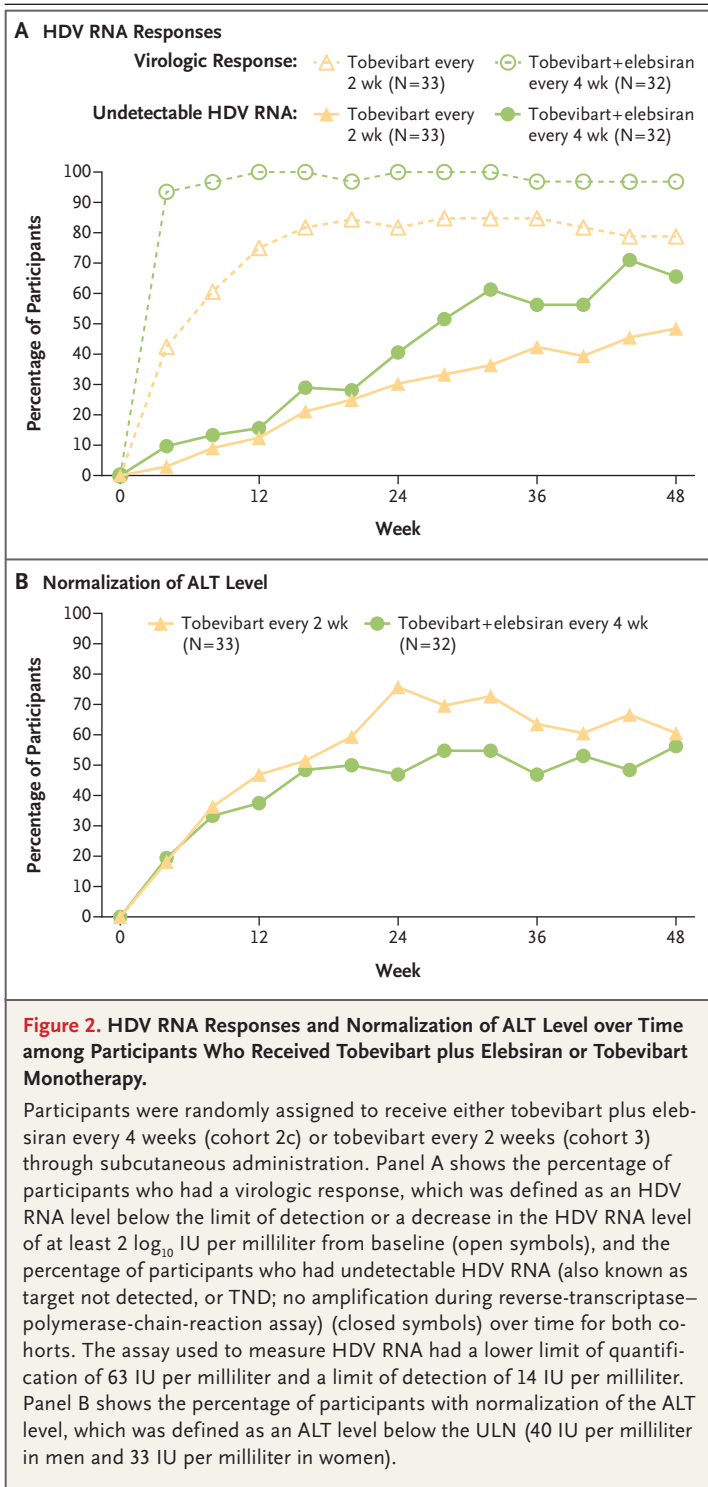
Table 2. Primary and Key Secondary End Points.*

Response	Week 24		Week 48	
	Tobevibart plus Elebsiran Every 4 Wk (N=32)	Tobevibart Every 2 Wk (N=33)	Tobevibart plus Elebsiran Every 4 Wk (N=32)	Tobevibart Every 2 Wk (N=33)
Combined response†				
No. of participants	15	23	18	20
Percentage of participants (95% CI)	47 (29–65)	70 (51–84)	56 (38–74)	61 (42–77)
According to cirrhosis status — no./total no. (%)				
Present	8/18 (44)	10/15 (67)	10/18 (56)	10/15 (67)
Absent	7/14 (50)	13/18 (72)	8/14 (57)	10/18 (56)
Undetectable HDV RNA‡				
No. of participants	13	10	21	16
Percentage of participants (95% CI)	41 (24–59)	30 (16–49)	66 (47–81)	48 (31–67)
According to cirrhosis status — no./total no. (%)				
Present	9/18 (50)	4/15 (27)	13/18 (72)	6/15 (40)
Absent	4/14 (29)	6/18 (33)	8/14 (57)	10/18 (56)
HDV RNA level below LOD or decrease of $\geq 2 \log_{10}$ IU/ml from baseline				
No. of participants	32	27	31	26
Percentage of participants (95% CI)	100 (89–100)	82 (65–93)	97 (84–100)	79 (61–91)
According to cirrhosis status — no./total no. (%)				
Present	18/18 (100)	13/15 (87)	17/18 (94)	12/15 (80)
Absent	14/14 (100)	14/18 (78)	14/14 (100)	14/18 (78)
Normalization of ALT level				
No. of participants	15	25	18	20
Percentage of participants (95% CI)	47 (29–65)	76 (58–89)	56 (38–74)	61 (42–77)
According to cirrhosis status — no./total no. (%)				
Present	8/18 (44)	10/15 (67)	10/18 (56)	10/15 (67)
Absent	7/14 (50)	15/18 (83)	8/14 (57)	10/18 (56)
HBsAg level <10 IU/ml				
No. (%)	28 (88)	7 (21)	29 (91)	7 (21)
According to cirrhosis status — no./total no. (%)				
Present	14/18 (78)	4/15 (27)	15/18 (83)	4/15 (27)
Absent	14/14 (100)	3/18 (17)	14/14 (100)	3/18 (17)

* HDV RNA was measured with the use of the RoboGene HDV DNA quantification kit, version 2.0, with manual RNA extraction. The assay has a lower limit of quantification of 63 IU per milliliter and a limit of detection (LOD) of 14 IU per milliliter. HBsAg was measured with the use of the Roche Elecsys HBsAg II assay, which has a lower limit of quantification of 0.05 IU per milliliter. CI denotes confidence interval.

† Combined response was defined as an HDV RNA level below the LOD or a decrease in the HDV RNA level of at least $\geq 2 \log_{10}$ IU per milliliter from baseline (virologic response) and normalization of the ALT level. Normalization of the ALT level was defined as a level below the upper limit of the normal range (40 IU per milliliter in men and 33 IU per milliliter in women). The primary end point was a combined response at week 24.

‡ Undetectable HDV RNA (also known as target not detected, or TND) was defined as no amplification during reverse-transcriptase–polymerase-chain-reaction assay.



cinoma that was considered by the investigator to be unrelated to treatment. Three participants in the tobeivart monotherapy cohort (the participant with hepatocellular carcinoma and two with mod-

erate influenza-like illness) discontinued treatment owing to adverse events. No participants receiving tobeivart plus elebsiran discontinued treatment owing to adverse events. Two participants had elevations in the ALT level of grade 3 or higher (one with elebsiran monotherapy and one in the tobeivart-plus-elebsiran rollover cohort). No elevations in the ALT level of grade 3 or higher were observed in participants who started tobeivart and elebsiran simultaneously or who received tobeivart monotherapy. Adverse-event narratives are provided in the Supplementary Appendix. Neutrophil-count abnormalities of grade 3 or higher were infrequent but appeared to be more common in the cohort receiving tobeivart every 2 weeks than in the cohorts with dose administration every 4 weeks. No deaths occurred.

DISCUSSION

In this ongoing phase 2 trial without formal hypothesis testing, a combined response (virologic response and normalization of the ALT level) at week 24 (primary end point) was observed in 47% of participants who received tobeivart plus elebsiran and in 70% of those who received tobeivart monotherapy. Through week 48, the SOLSTICE trial provides evidence that tobeivart plus elebsiran, which directly target HBsAg, can reduce HDV RNA and HBsAg levels and normalize ALT levels. Tobeivart and elebsiran independently appear to have potent antiviral activity and, when combined, have complementary activity that appears to decrease HDV viremia to undetectable HDV RNA (no amplification during RT-PCR assay) with dose administration every 4 weeks.

Undetectable HDV RNA has emerged as the most important surrogate end point in HDV drug development because it is the most robust virologic efficacy measure and is associated with long-term HDV control.^{12,15,16} In the SOLSTICE trial, 41% of participants who received tobeivart plus elebsiran had undetectable HDV RNA at week 24, and the percentage increased to 66% at week 48. In clinical trials of bulevirtide, undetectable HDV RNA during treatment was observed in 12% of participants receiving 2 mg per day (approved dose) and in 20% of those receiving 10 mg per day (not approved; highest dose evaluated) at week 48. When bulevirtide was administered with weekly peginterferon alfa for 48 weeks followed by bule-

virtide monotherapy for an additional 48 weeks (96 week total treatment duration), the percentages of participants with undetectable HDV RNA at 48 weeks after the end of treatment were 26% with 2-mg bulevirtide and 46% with 10-mg bulevirtide.^{12,15}

At week 24 in the SOLSTICE trial, the percentage of participants with normalization of the ALT level was lower with tobevibart plus elebsiran than with tobevibart (47% vs. 76%). At week 48, the percentages were similar in the two cohorts (56% and 61%, respectively). Of note, undetectable HDV RNA was not always associated with normalization of the ALT level, with some participants maintaining persistent low-level elevation in the ALT level despite HDV RNA suppression. Fluctuations in the ALT level are observed in patients with chronic HDV infection, and the role of other etiologic factors (e.g., chronic HBV infection or a nonspecific reaction to siRNA in HDV infection) is difficult to ascertain.²³ In both cohorts, participants without normalization of the ALT level had decreases in the level, which plateaued at less than 1.25 times the upper limit of the normal range. ALT levels then remained consistent, and no ALT flares occurred in participants who started tobevibart and elebsiran simultaneously or who received tobevibart monotherapy. ALT flares have been observed in participants with chronic HDV infection receiving regimens containing siRNA (REEF-D trial²⁴; also see the adverse-event narrative in the Supplementary Appendix). Whether tobevibart, when administered with elebsiran, ameliorates low-level elevations in the ALT level that can occur with siRNA monotherapy remains unknown.

HDV requires the presence of HBsAg to complete its replication cycle.¹ In the SOLSTICE trial, an HBsAg level below 10 IU per milliliter (the target for HBV therapies) was observed in 91% of participants who received tobevibart plus elebsiran. This high incidence of response may be attributable to the complementary mechanisms of tobevibart and elebsiran.^{18-21,25} The complementary mechanisms and profound suppression of HBsAg could have additional benefits, including more stable long-term HDV suppression with an extended dose-administration interval and possible boosting of HBsAg-targeting immunity and clearance of infected hepatocytes.

Most adverse events were mild or moderate across treatment groups; transient influenza-like

Table 3. Summary of Safety Assessments in Participants through Week 48.*

Event	Tobevibart plus Elebsiran Every 4 Wk (N=32)	Tobevibart Every 2 Wk (N=33)
	no. of participants (%)	
Any adverse event	26 (81)	31 (94)
Grade 1 or 2: mild or moderate	26 (81)	29 (88)
Grade 3: severe	0	1 (3)†
Grade 4: life-threatening	0	1 (3)‡
Adverse events in >10% of participants in either group		
Chills	8 (25)	8 (24)
Influenza-like illness	8 (25)	10 (30)
Pyrexia	7 (22)	3 (9)
Headache	6 (19)	7 (21)
Fatigue	2 (6)	4 (12)
Myalgia	2 (6)	8 (24)
Dizziness	1 (3)	4 (12)
Nausea	1 (3)	4 (12)
Treatment-related adverse event	23 (72)	26 (79)
Related to elebsiran	22 (69)	—
Related to tobevibart	22 (69)	25 (76)
Any serious adverse event	0	1 (3)†
Influenza-like symptoms§	22 (69)	24 (73)
Injection-site reaction	3 (9)	1 (3)
Adverse event leading to interruption of trial drug	0	1 (3)
Adverse event leading to discontinuation of trial drug	0	3 (9)†¶
Adverse event leading to death	0	0
Grade 3 or 4 laboratory abnormalities: neutrophil count <1000/mm ³	3 (9)	5 (15)

* Shown are adverse events that emerged or worsened on or after the date of the start of the trial drug up to 30 days after permanent discontinuation of the trial drug. A participant with multiple events within a category is counted only once in that category. Safety data for participants from the monotherapy and rollover cohorts are reported in Tables S9 and S10.

† One participant had hepatocellular carcinoma at day 192, which was considered by the investigator to be unrelated to tobevibart. More details are provided in the adverse-event narratives in the Supplementary Appendix.

‡ One participant had several instances of grade 3 and 4 neutropenia, which lessened in severity to grade 2 to 3 without treatment and were considered by the investigator to be related to tobevibart. This participant also received tobevibart plus elebsiran every 4 weeks as part of the 2c rollover cohort and had grade 3 neutropenia on day 4 of combination therapy. More details are provided in the adverse-event narratives in the Supplementary Appendix.

§ Influenza-like symptoms include arthralgia, chills, fatigue, fever, headache, influenza-like illness, myalgia, and pyrexia. The majority of participants had these adverse events only on day 1 after receiving the first dose of the trial drug, and they resolved spontaneously within 24 to 48 hours.

¶ Two participants had moderate influenza-like illness, which was considered by the investigator to be related to tobevibart, on the day of the first dose of tobevibart. The symptoms resolved within 24 hours.

illness and chills were the most common. Influenza-like symptoms have been observed with other monoclonal antibodies.²⁶ Together, the efficacy and safety data provide evidence highlighting the potential of tobevibart plus elebsiran in managing chronic HDV, including in patients with compensated cirrhosis.

Strengths of the trial include a flexible design that enabled evaluation of different regimens across a broad participant population for future investigation,²⁷ which led to the addition of a cohort receiving tobevibart every 2 weeks. Further exploration of elebsiran monotherapy in a broad population of persons with HDV infection was deferred owing to emerging data from cohort 1a and the REEF-D trial²⁴ on the risk of ALT flares. Participants were well balanced with respect to sex and compensated cirrhosis, and participants with high baseline levels of HDV RNA and HBsAg were included. HBV replication was controlled in all the participants with nucleoside or nucleotide therapy. Limitations include the open-label design, small sample, lack of formal hypothesis testing, limited number of participants who did not have HDV genotype 1 (which potentially limits the generalizability of the findings), and lack of a placebo comparator.

The phase 3 ECLIPSE program with the tobevibart-plus-elebsiran regimen is ongoing. Three global studies (ClinicalTrials.gov numbers, NCT06903338, NCT07128550, and NCT07142811) are further evaluating safety, efficacy, and long-term clinical outcomes in participants with chronic HDV infection, including those with compensated cirrhosis.²⁸ In addition, finite therapy with tobevibart plus elebsiran is planned to be evaluated in two of these studies.

The SOLSTICE trial, although not designed for formal hypothesis testing, provides evidence sug-

gesting that tobevibart plus elebsiran, which directly targets HBsAg, can reduce HDV RNA and HBsAg levels and normalize ALT levels. Through week 48, tobevibart and elebsiran appeared to independently show potent antiviral activity and, when combined, may prove to be an effective monthly treatment option for chronic HDV infection. Tobevibart plus elebsiran appeared to result in decreases in HDV RNA and HBsAg levels, with undetectable HDV RNA in 66% of participants at week 48. ALT flares were infrequent (none occurred in participants who started tobevibart and elebsiran simultaneously or who received tobevibart monotherapy) but warrant monitoring. The phase 3 ECLIPSE program will further evaluate the regimen in participants with HDV infection.

Supported by Vir Biotechnology.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Kiley Margolis, Pharm.D., and Jeanne McKeon, Ph.D., of Humanity Communications, for writing the first draft of the manuscript under the direction of the authors and in accordance with Good Publication Practice guidelines.

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