Efficacy and Safety of Tobevibart (VIR-3434) Alone or in Combination With Elebsiran (VIR-2218) in Participants With Chronic Hepatitis Delta Virus Infection: Week 48 Endpoint Analysis From the Phase 2 SOLSTICE Trial

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Disclosures

- **Tarik Asselah** reports serving as an expert speaker and investigator for AbbVie, Antios Therapeutics, Eiger BioPharmaceuticals, ENYO Pharma, Gilead Sciences, GSK, Janssen, Roche, and Vir Biotechnology, Inc.
- **Anca Streinu-Cercel** reports receiving honoraria from Gilead Sciences, Janssen, Merck Sharp & Dohme, and Moderna; support for meeting travel from Gilead Sciences and MSD; and serving as an advisory board member for Gilead Sciences, Immunocore, Moderna, and ViiV Healthcare
- **Alina Jucov** reports serving as an advisory board member for Vir Biotechnology, Inc.
- **Edward Gane** reports receiving grant/research support from AbbVie; speaker fees from AbbVie; advisor fees from Aligos Therapeutics, Assembly Biosciences, Gilead Sciences, Janssen, Precision, Roche, Tune, Vir Biotechnology, Inc., and Virion Therapeutics
- **Heiner Wedemeyer** reports receiving research funding from Gilead Sciences, RoboGene, and Roche; consultant fees from Abbott, AbbVie, Falk, Gilead Sciences, GSK, Janssen, Roche, and Vir Biotechnology, Inc.; and serving as an expert speaker for Gilead Sciences
- **Pietro Lampertico** reports serving as an advisory board or speaker bureau member for AbbVie, Aligos Therapeutics, Alnylam, altona Diagnostics, Antios Therapeutics, Arrowhead, Bristol Myers Squibb, Eiger BioPharmaceuticals, Gilead Sciences, Grifols, GSK, Janssen, MSD, MYR Pharmaceuticals, Roboscreen, Roche, Spring Bank, and Vir Biotechnology, Inc.
- **Michael A. Chattergoon**, **Brianna L. Bullard**, **Yimeng Lu**, **Cheng Huang**, **Rima Acosta**, **Cara Pilowa**, and **Todd Correll** are employees of Vir Biotechnology, Inc. and may own stock in Vir Biotechnology, Inc.
- **Kosh Agarwal** reports receiving grant/research support from Gilead Sciences; speaker fees from Gilead Sciences, GSK, Janssen, and Sobi; consultant fees from Aligos Therapeutics, Arbutus, Assembly Biosciences, Boehringer Ingelheim, Bristol Myers Squibb, Drug Farm, Gilead Sciences, GSK, Janssen, Roche, Sagimet Biosciences, and Vir Biotechnology, Inc.

Background

- Chronic hepatitis delta (CHD) causes the most severe form of chronic viral hepatitis leading to high rates of cirrhosis and hepatocellular carcinoma[1]
- Up to 12 million people are living with HDV worldwide, with up to 80% of patients progressing to cirrhosis within 5 to 10 years[2,3]
- Achieving HDV RNA target not detected (TND) may be associated with long-term clinical outcome improvement and lower risk of off treatment relapse
- As previously reported, elebsiran and tobevibart monotherapy and combination cohorts in SOLSTICE demonstrated reductions in HDV RNA and HBsAg
- Here, we present Phase 2 SOLSTICE Week 48 results for tobevibart + elebsiran, an investigational combination therapy for the treatment of chronic HDV infection

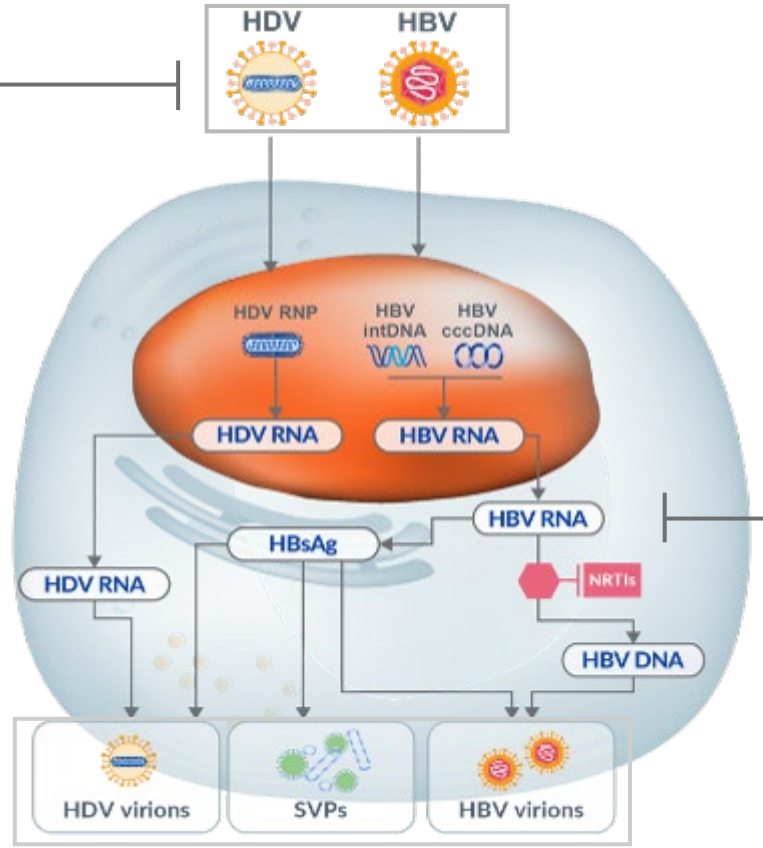
HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; TND, target not detected.
HDV RNA TND = undetectable HDV RNA

1. World Health Organization. Hepatitis D. July 2023. Accessed May 30, 2024. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d.
2. Asselah T, Rizzetto M. *N Eng J Med*. 2023;389(1):58-70.
3. Pan C, et al. *Dig Dis Sci*. 2023;68(8):3237-3248.

Tobevibart and Elebsiran Mechanisms of Action

Tobevibart[1] (VIR-3434, mAb)

Inhibition of viral entry (neutralization)



Elebsiran[2] (VIR-2218, siRNA)

Reduction of HBV RNA

Tobevibart[1] (VIR-3434, mAb)

Clearance of viral and SVPs

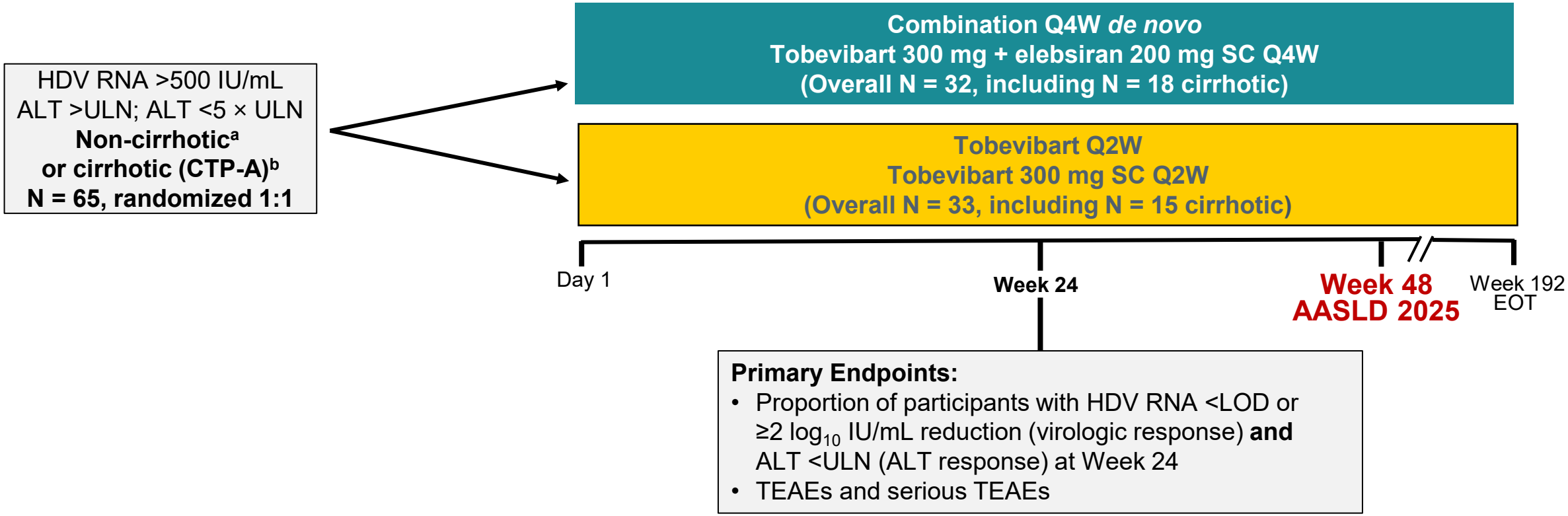
Tobevibart, a mAb, and elebsiran, an siRNA, have complementary mechanisms of action against HDV and HBV

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cccDNA, covalently closed circular DNA; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; intDNA, integrated DNA; mAb, monoclonal antibody; NRTI, nucleos(t)ide reverse transcriptase inhibitor; RNP, ribonucleoprotein; siRNA, small interfering RNA; SVP, subviral particle.

1. Lempp FA, et al. *J Hepatol*. 2023;79(5):1129-1138. 2. Gane E, et al. *J Hepatol*. 2023;79(4):924-932.

SOLSTICE Study Design: Tobevibart + Elebsiran Q4W and Tobevibart Q2W in Participants Living With Chronic HDV infection



SOLSTICE ClinicalTrials.gov Identifier: NCT05461170.
ALT, alanine aminotransferase; CHD, chronic hepatitis delta; CTP, Child-Turcotte-Pugh; EOT, end of treatment; HDV, hepatitis D virus; LOD, limit of detection; NRTI, nucleos(t)ide reverse transcriptase inhibitor; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
[a]Non-cirrhotic: liver biopsy with METAVIR F0 to F3 or liver stiffness <12 kPa within 12 months of screening and platelet count >150 × 10^3/μL.
[b]Compensated cirrhotic participants: liver biopsy with METAVIR F4 or liver stiffness ≥12 kPa within 12 months of screening, a platelet count >90 × 10^3/μL, and a CTP score of 5 or 6, inclusive at screening and at the start of the study.

Participant Demographic and Baseline Characteristics[a]

	Tobevibart + elebsiran Q4W *de novo* N = 32	Tobevibart Q2W N = 33
Age, y, mean ± SD	41.5 ± 8.0	44.8 ± 9.2
Male, n (%)	18 (56.3)	16 (48.5)
Race, n (%)		
White	25 (78.1)	28 (84.8)
Black or African American	4 (12.5)	2 (6.1)
Asian	2 (6.3)	1 (3.0)
Other	1 (3.1)	2 (6.1)
ALT, U/L, mean ± SD	83.4 ± 47.1	75.7 ± 58.8
HDV RNA, log_{10} IU/mL, mean ± SD	5.7 ± 1.2	5.6 ± 1.1
HDV genotype, gt (%)	gt1 (97%); gt5 (3%)	gt1 (97%); gt5 (3%)
HBsAg, log_{10} IU/mL, mean ± SD	3.7 ± 0.6	3.7 ± 0.8
HBeAg positive, n (%)	3 (9.4)	8 (24.2)
HBV DNA, log_{10} IU/mL, mean ± SD	0.7 ± 0.7	0.7 ± 0.8
Cirrhotic participants, n (%)	18 (56.3)	15 (45.5)
Platelets, 10^9/L, mean ± SD	189.4 ± 58.0	200.2 ± 74.5
Liver stiffness, kPa, mean ± SD	13.5 ± 7.3	13.5 ± 8.7
FibroTest score, mean ± SD	0.5 ± 0.3	0.5 ± 0.2

Demographic and baseline characteristics were generally balanced across the treatment groups

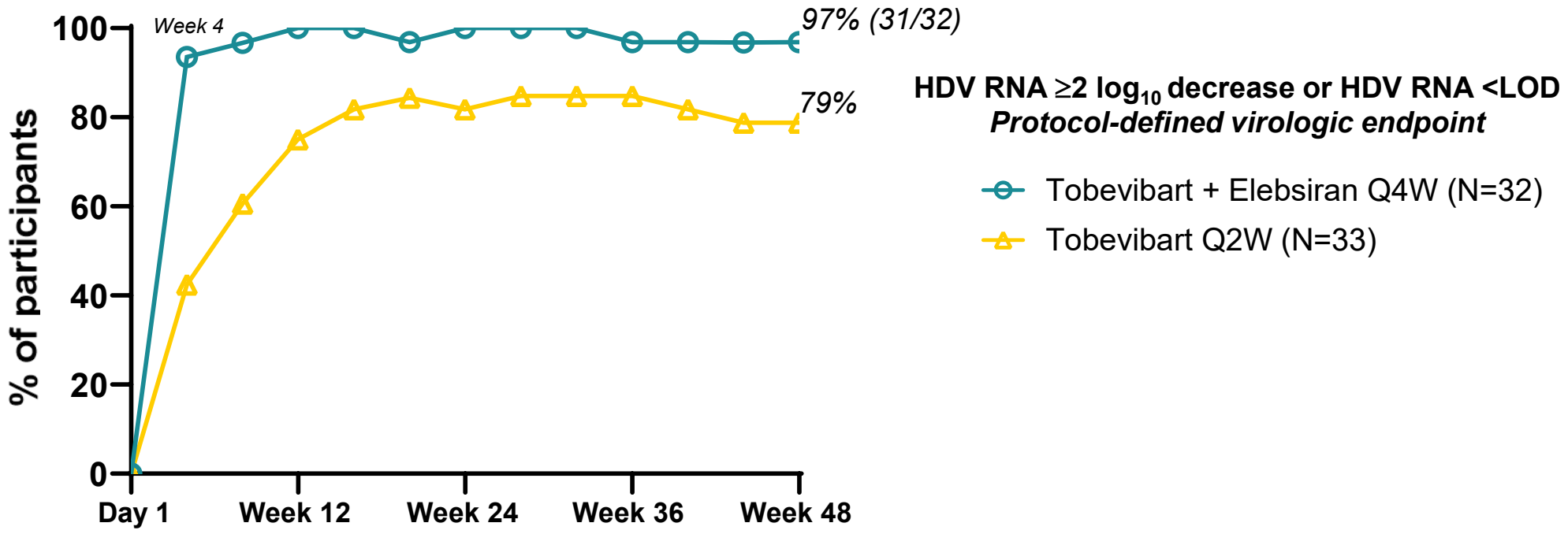
[a]All participants remained on concomitant NA therapy throughout the duration of the study.
ALT, alanine aminotransferase; gt, genotype; HBeAg, hepatitis e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; LOD, limit of detection; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogues; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SD, standard deviation.
HDV RNA was measured using RoboGene 2.0 with manual RNA extraction; HDV RNA LLOQ = 63 IU/mL; HDV RNA LOD = 14 IU/mL.

Data Published in New England Journal of Medicine

A Phase 2 Trial of Tobevibart plus Elebsiran in Hepatitis Delta

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- https://www.nejm.org/doi/full/10.1056/NEJMoa2508827

Higher Antiviral Responses in Participants Receiving Tobevibart + Elebsiran Through Week 48

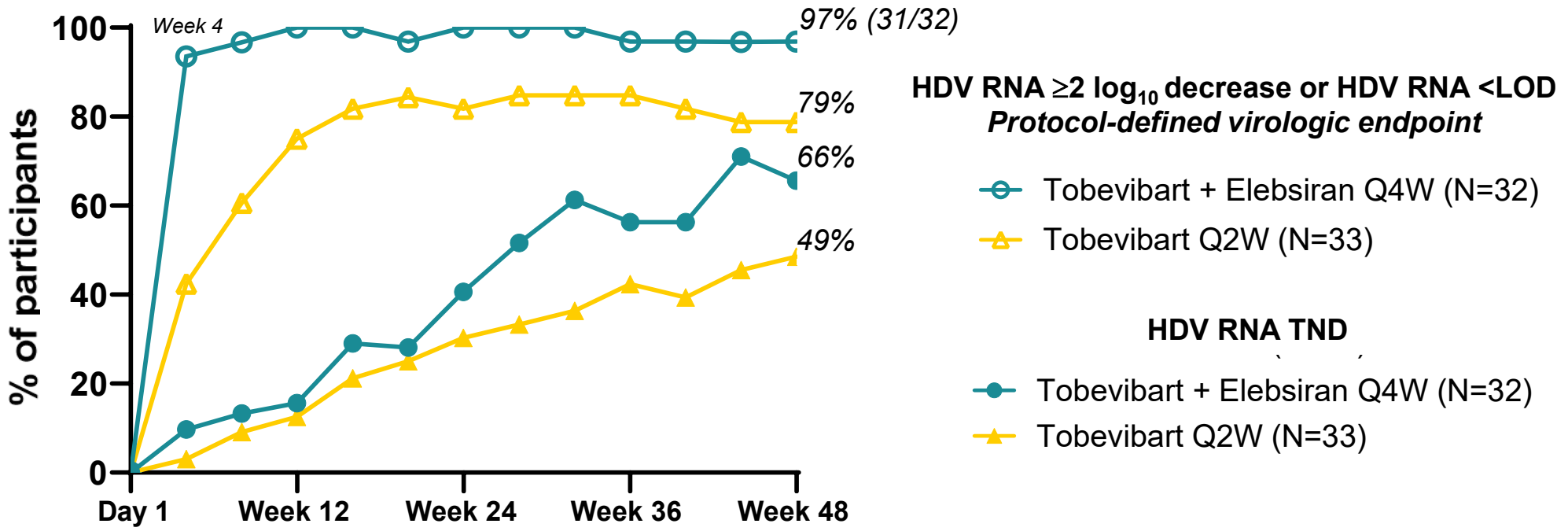


Participants receiving tobevibart + elebsiran more rapidly suppressed HDV RNA to a ≥2 log_{10} decrease from baseline or HDV RNA <LOD

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HDV, hepatitis D virus; LOD, limit of detection; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TND, target not detected.
Data are reported for participants who completed the visit and had an HDV RNA measurement or who discontinued treatment before the visit.
HDV RNA LOD = 14 IU/mL; HDV RNA TND = undetectable HDV RNA

Higher Antiviral Responses in Participants Receiving Tobevibart + Elebsiran Through Week 48

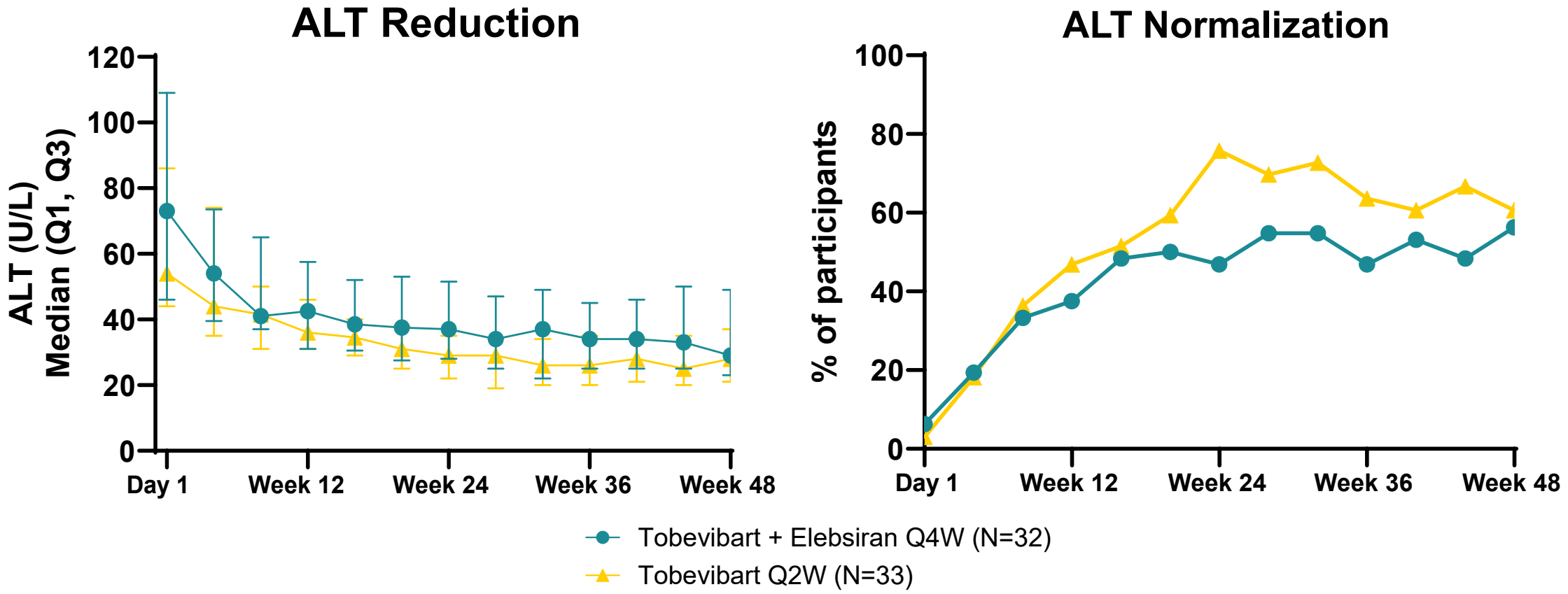


A larger proportion of the tobevibart + elebsiran cohort achieved HDV RNA TND vs tobevibart monotherapy. The number of participants reaching HDV RNA TND increased steadily through Week 48

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HDV, hepatitis D virus; LOD, limit of detection; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TND, target not detected.
Data are reported for participants who completed the visit and had an HDV RNA measurement or who discontinued treatment before the visit.
HDV RNA LOD = 14 IU/mL; HDV RNA TND = undetectable HDV RNA.

Similar Reductions in ALT Were Observed

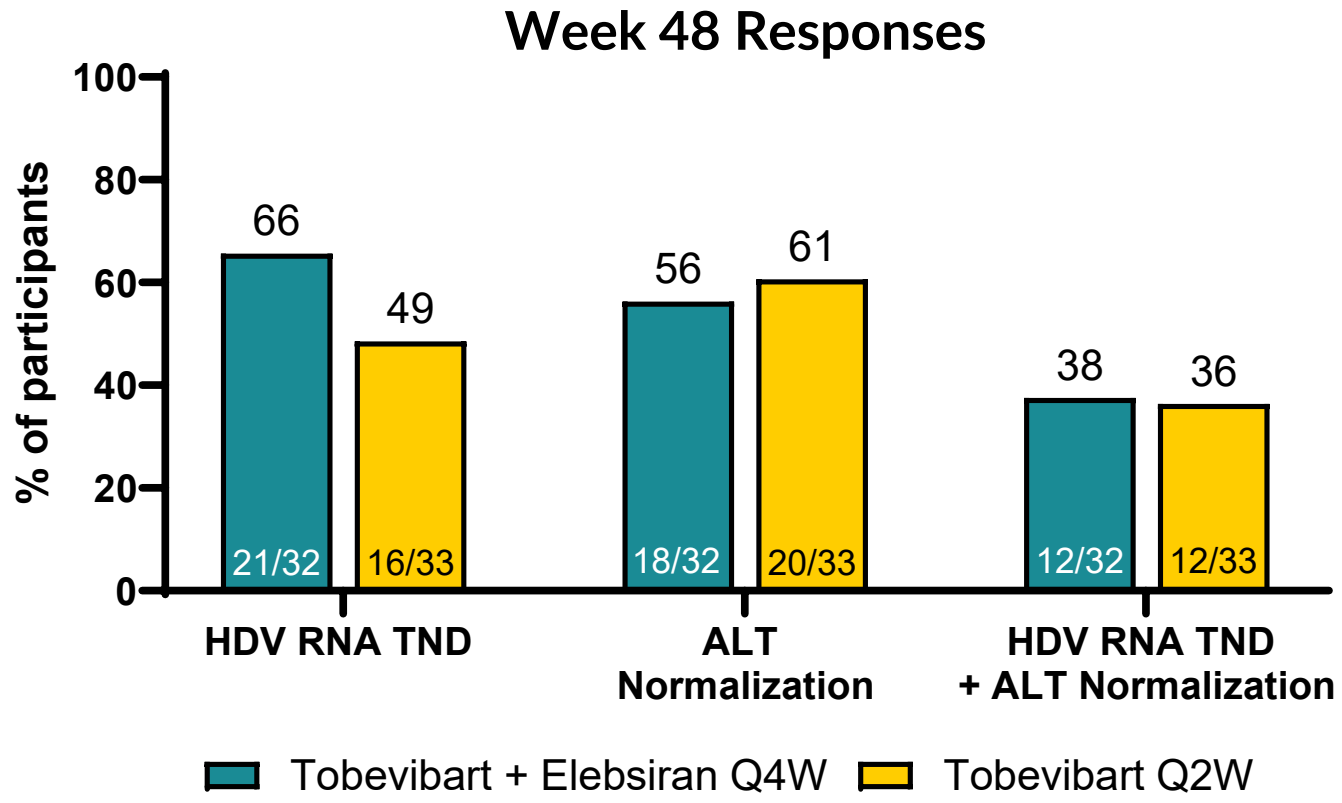


ALT normalization at Week 48 was similar between tobevibart + elebsiran and tobevibart monotherapy

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ALT, alanine aminotransferase; Q2W, once every 2 weeks; Q4W, once every 4 weeks; ULN, upper limit of normal.
Data are reported for participants who completed the visit and had an ALT measurement or who discontinued treatment before the visit.
ALT ULN (male) = 40 IU/mL; ALT ULN (female) = 33 IU/mL.

Similar Combined Responses (HDV RNA TND + ALT Normalization) Largely Driven by Similar ALT Responses

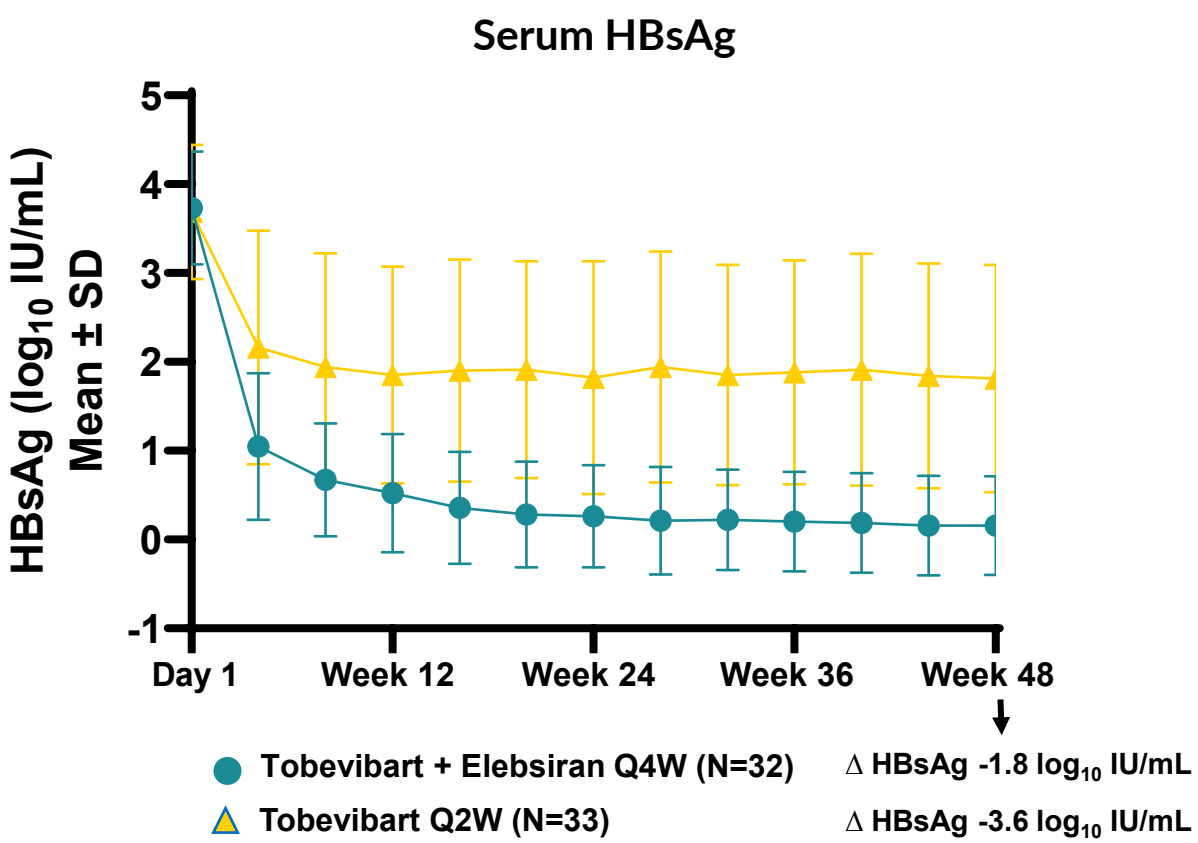


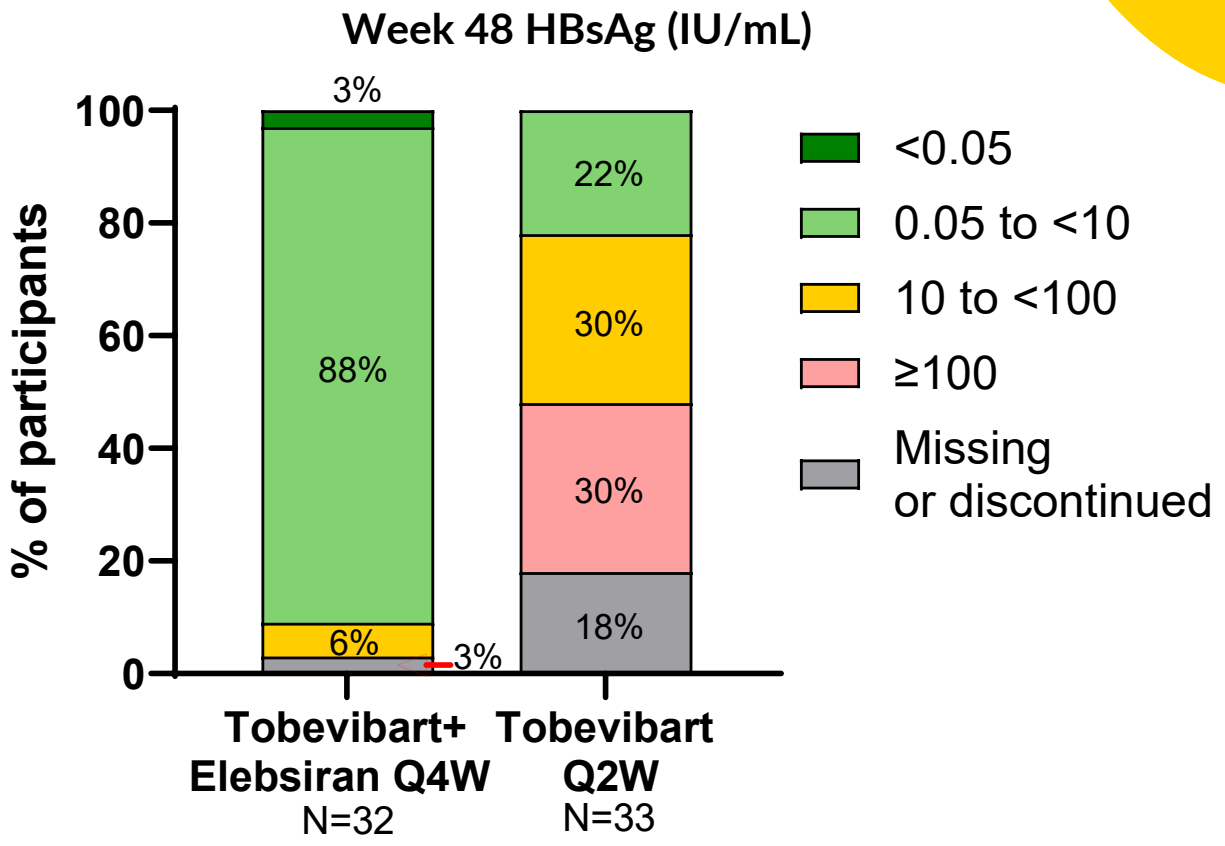
Combined response rates are largely driven by similar ALT normalization rates, despite a higher proportion of tobevibart + elebsiran participants achieving HDV RNA TND

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ALT, alanine aminotransferase; HDV, hepatitis D virus; LOD, limit of detection; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TND, target not detected; ULN, upper limit of normal.
Data are reported for participants who completed the visit and had an HDV RNA measurement or who discontinued treatment before the visit.
HDV RNA LOD = 14 IU/mL; HDV RNA TND = undetectable HDV RNA; ALT ULN (male) = 40 IU/mL; ALT ULN (female) = 33 IU/mL.

Tobevibart + Elebsiran Combination Led to Greater Reduction in HBsAg





Approximately 90% of participants receiving tobevibart + elebsiran achieved HBsAg values <10 IU/mL at Week 48

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HBsAg, hepatitis B surface antigen; Q2W, once every 2 weeks; Q4W; once every 4 weeks.
Data are reported for participants who completed the visit and had an HBsAg measurement or who discontinued treatment before the visit.

Majority of Adverse Events Were Grade 1 or 2 and Transient Through Week 48

Safety or tolerability measure, n (%)[a]	Tobevibart + elebisran Q4W *de novo* N = 32	Tobevibart Q2W N = 33
Any TEAE	26 (81)	31 (94)
Grade 1-2	26 (81)	29 (88)
Grade 3	0	1 (3)[b]
Grade 4	0	1 (3)[c]
Treatment-related TEAE	23 (72)	26 (79)
Treatment-emergent influenza-like symptoms[d]	22 (69)	25 (76)
Treatment-emergent injection-site reactions[e]	4 (13)	4 (12)
TEAE leading to study drug interruption	0	1 (3)[f]
TEAE leading to study drug discontinuation	0	3 (9)[g]
Serious TEAE	0	1 (3)[b]
Treatment-related serious TEAE	0	0

Most TEAEs were grade 1 or 2 across treatment groups, and the most common TEAE (influenza-like illness) was generally mild to moderate and transient

Q2W, once every 2 weeks; Q4W, once every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]A participant with multiple events within a category is counted only once in that category.
[b]Grade 3 hepatocellular carcinoma (SAE) deemed unrelated to study drugs by investigator.
[c]Grade 4 neutropenia on Week 12 and Week 16; recovered to grade 2 or 3 after Week 16 without treatment.
[d]Influenza-like symptoms included arthralgia, chills, fatigue, fever, headache, influenza-like illness, myalgia, and pyrexia.
[e]Injection-site reactions included pain, pruritus, erythema, swelling.
[f]Reason for study drug interruption: neutropenia (Preferred term).
[g]Reason for discontinuation: 2 cases of influenza-like illness (Preferred term) and 1 case of hepatocellular carcinoma.

Summary of Key Findings

- Higher maintained rates of HDV RNA TND were observed with tobevibart + elebsiran across a diverse patient population
- ALT normalization at Week 48 was similar between combination and monotherapy cohorts leading to similar combined response rates
- Tobevibart + elebsiran showed high reductions in serum HBsAg
- Reported adverse events were generally mild to moderate and transient with few study-related discontinuations and no related SAEs

In conclusion, at Week 48, tobevibart + elebsiran achieved the highest rate of HDV RNA TND, with similar rates of ALT normalization with a generally well-tolerated safety profile

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; SAE, serious adverse event; TND, target not detected.
HDV RNA TND = undetectable HDV RNA.

Comprehensive Phase 3 ECLIPSE Program

Tobevibart + elebsiran is now being evaluated in a comprehensive Phase 3 program in patients with chronic HDV infection

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