

Efficacy and Safety of Tobeivibart (VIR-3434) Alone or in Combination With Elebsiran (VIR-2218) in Participants With Chronic Hepatitis Delta Virus Infection: Week 96 Endpoint Analysis From the Phase 2 SOLSTICE Trial

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Background

- Chronic hepatitis delta infection causes the most severe form of chronic viral hepatitis leading to high rates of cirrhosis, decompensation, and hepatocellular carcinoma¹
- 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
- Previously reported Week 48 results from the ongoing Phase 2 SOLSTICE study showed high rates of HDV RNA TND (66%) and reductions in ALT and HBsAg with tobevibart + elebsiran therapy⁴
- Here, we present SOLSTICE data through Week 96 for tobevibart + elebsiran, an investigational combination therapy for the treatment of chronic HDV infection

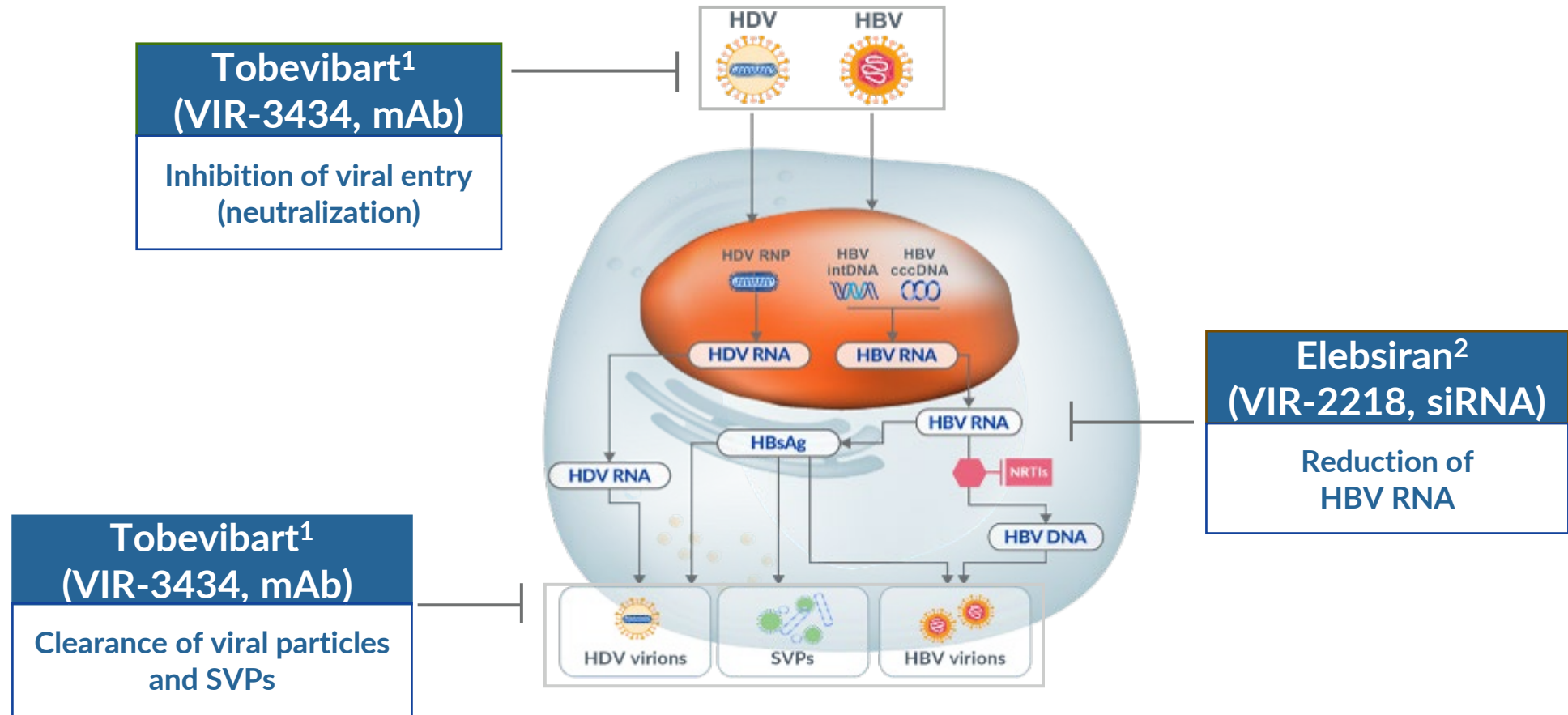
ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; TND, target not detected.

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.

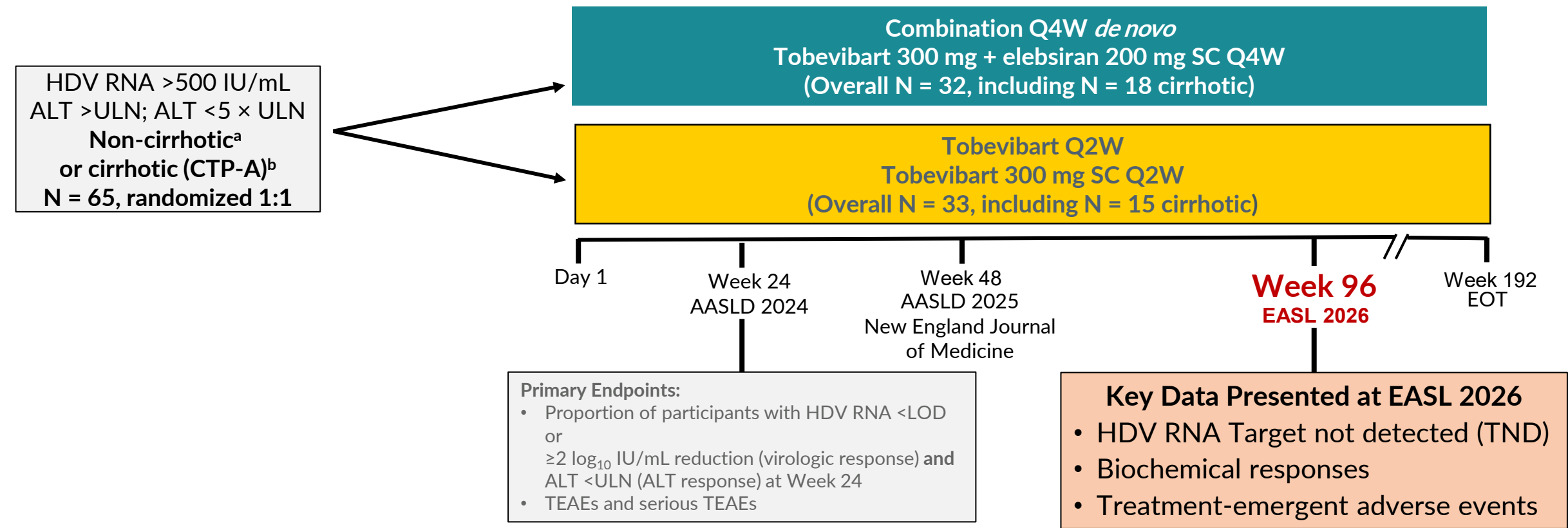
3. Pan C, et al. *Dig Dis Sci*. 2023;68(8):3237-3248. 4. Asselah, et al. *NEJM*. 2026;394:343-353

Tobevibart and Elebsiran Mechanisms of Action



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

SOLSTICE Study Design: Tobeivibart + Elebsiran Q4W and Tobeivibart 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.
HDV RNA was measured using RoboGene 2.0 with manual RNA extraction; HDV RNA LLOQ = 63 IU/mL; HDV RNA LOD = 14 IU/mL.
^aNon-cirrhotic: liver biopsy with METAVIR F0 to F3 or liver stiffness <12 kPa within 12 months of screening and platelet count >150 × 10³/μL.
^bCompensated cirrhotic participants: liver biopsy with METAVIR F4 or liver stiffness ≥12 kPa within 12 months of screening, a platelet count >90 × 10³/μL, and a CTP score of 5 or 6, inclusive at screening and at the start of the study.

Participant Demographic and Baseline Characteristics

	Tobevibart + elebsiran Q4W <i>de novo</i> 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	0.74 ± 0.66	0.71 ± 0.80
Cirrhotic participants ^a , 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	0.48 ± 0.25	0.45 ± 0.23

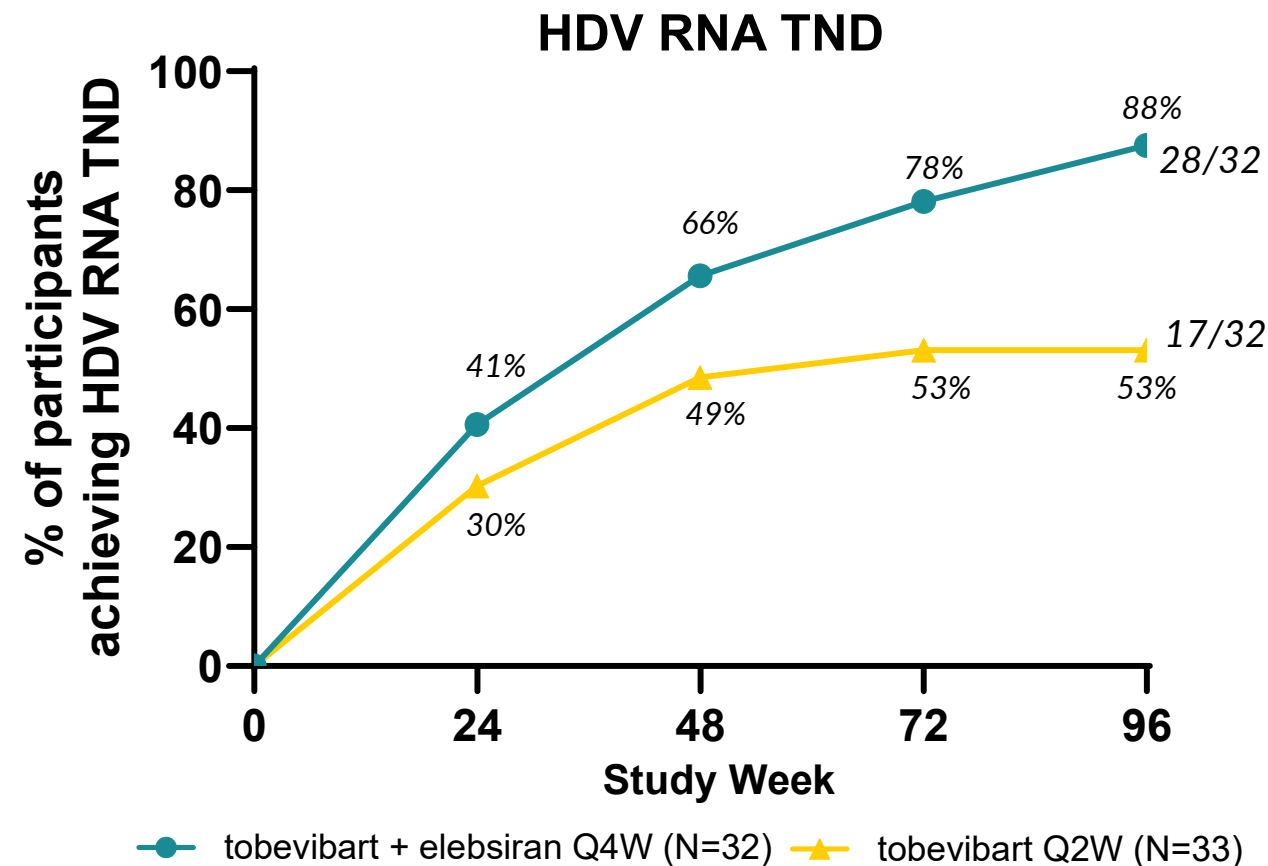
Demographic and baseline characteristics were generally balanced across the treatment groups.
All participants remained on concomitant NA therapy throughout the duration of the study.

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.

^a Two participants were classified as cirrhotic based on a liver biopsy; all other participants were classified by Fibroscan at screening.

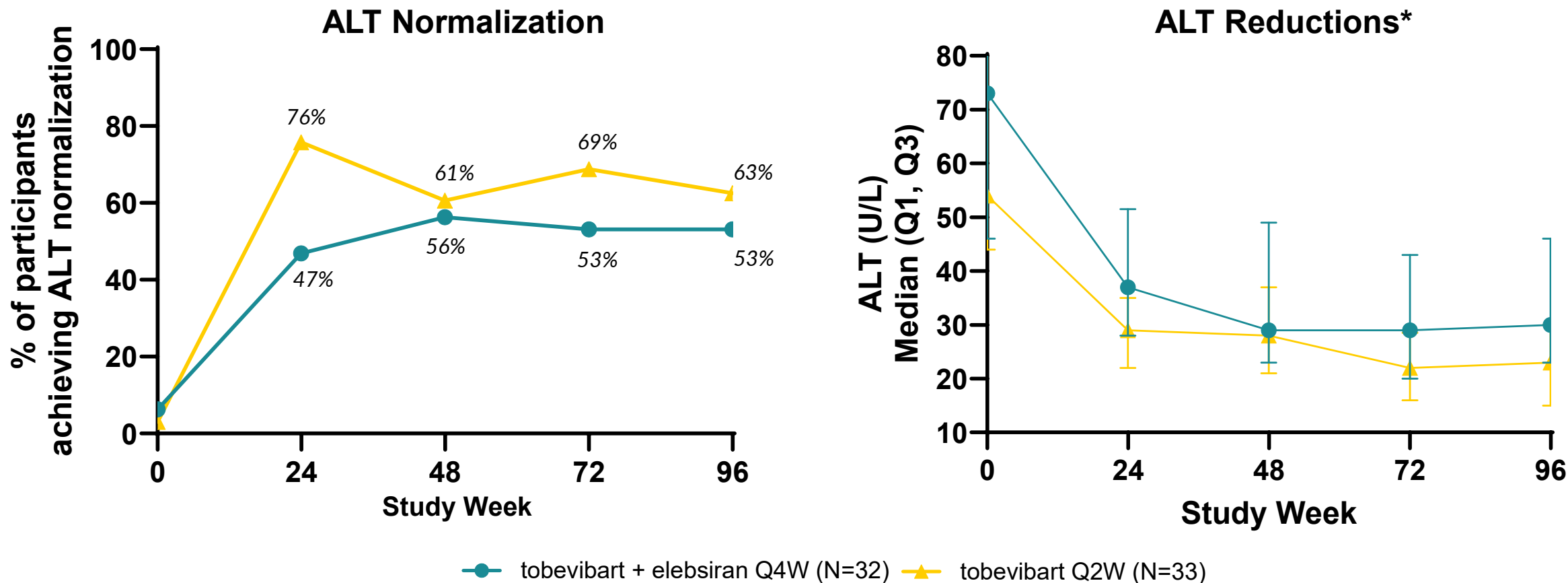
Tobevibart + Elebsiran Substantially Increases the Ability to Achieve HDV RNA TND at 96 Weeks (M=F analysis)



88% of participants receiving tobevibart + elebsiran achieved HDV RNA TND at Week 96. In contrast, rates of HDV RNA TND in the tobevibart cohort plateaued after Week 48.

HDV, hepatitis D virus; LOD, limit of detection; M=F analysis, missing equal failure analysis; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TND, target not detected. HDV RNA LOD = 14 IU/mL; HDV RNA TND = undetectable HDV RNA (no amplification during RT-PCR). By Week 96, 4 participants in the tobevibart+elebsiran Q4W cohort and 7 in the tobevibart Q2W cohort had discontinued treatment and are counted as failures in analysis; 1 participant receiving tobevibart Q2W is censored after week 52.

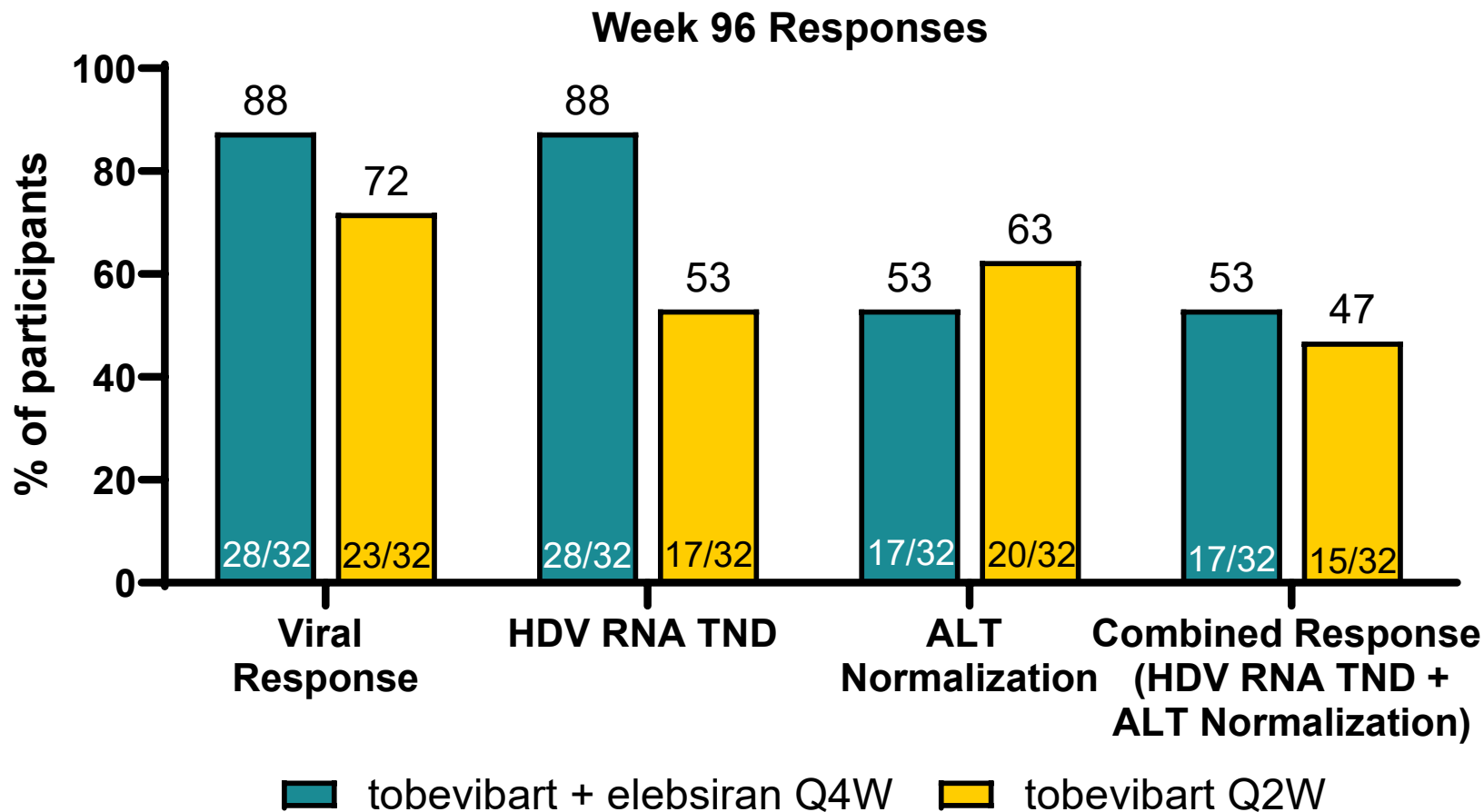
ALT Normalization Rates at Week 96 were Similar Between Cohorts and Consistent with Week 48 Results (M=F analysis)



Participants receiving tobevibart + elebsiran have robust reductions in ALT over time

ALT, alanine aminotransferase; M=F analysis, missing equal failure analysis; Q2W, once every 2 weeks; Q4W, once every 4 weeks; ULN, upper limit of normal. ALT ULN (male) = 40 IU/mL; ALT ULN (female) = 33 IU/mL. By Week 96, 4 participants in the tobevibart+elebsiran Q4W cohort and 7 in the tobevibart Q2W cohort had discontinued treatment and are counted as failures in analysis; 1 participant receiving tobevibart Q2W is censored after week 52. *One participant experienced a transient ALT elevation of Grade 2; All other ALT elevations were ≤Grade 1

Similar Combined Response (HDV RNA TND + ALT Normalization) in Both Cohorts Were Driven by Similar ALT Responses (M=F Analysis)



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

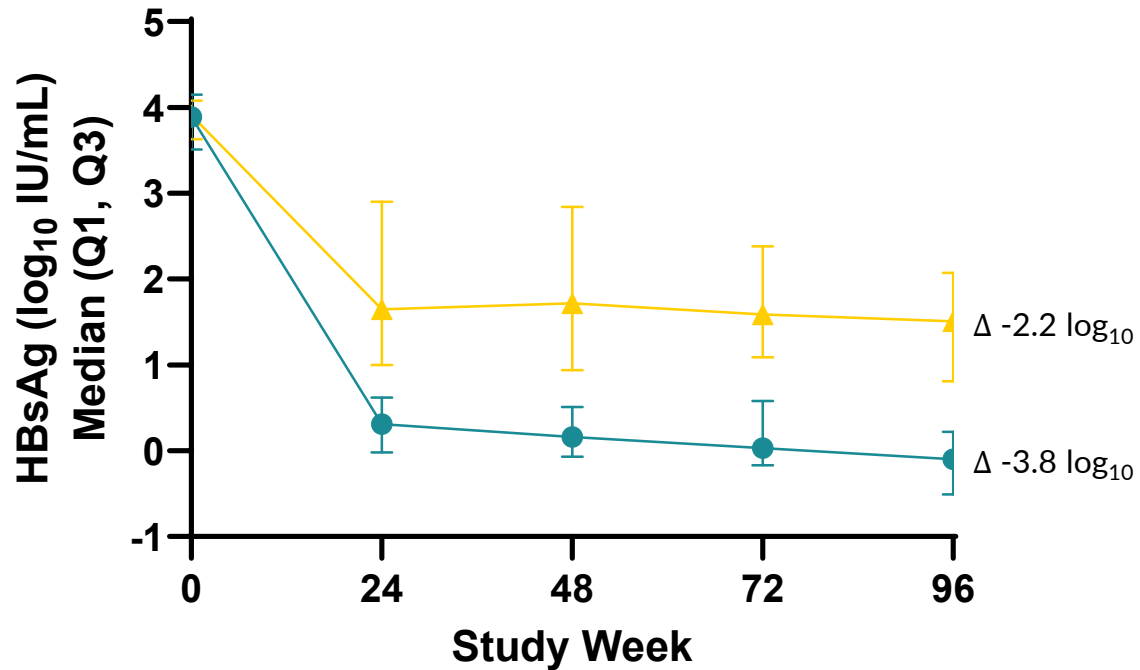
ALT, alanine aminotransferase; HDV, hepatitis D virus; M=F analysis, missing equal failure analysis; Q2W, once every 2 weeks; Q4W, once every 4 weeks; HDV RNA TND = undetectable HDV RNA (no amplification during RT-PCR); ULN, upper limit of normal. ALT ULN (male) = 40 IU/mL; ALT ULN (female) = 33 IU/mL.

By Week 96, 4 participants in the tobevibart+elebsiran Q4W cohort and 7 in the tobevibart Q2W cohort had discontinued treatment and are counted as failures in analysis; 1 participant receiving tobevibart Q2W is censored after week 52.

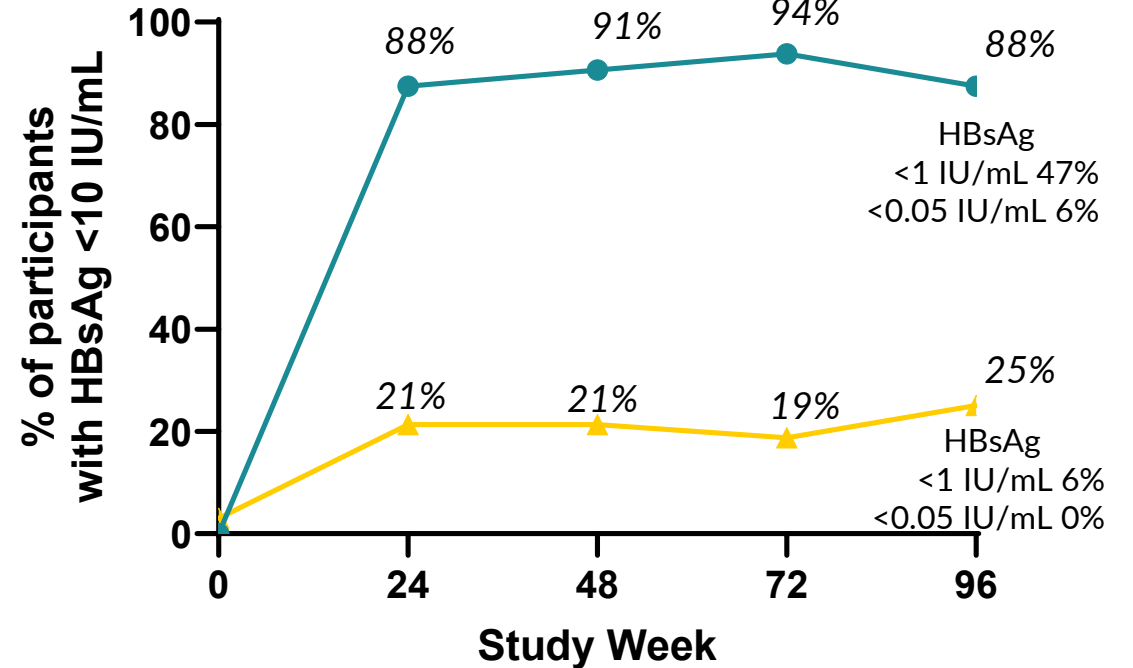
Viral Responses is defined as HDV RNA <LOD or $\geq 2 \log_{10}$ IU/mL reduction from baseline

Tobevibart + Elebsiran Rapidly Reduces HBsAg Over Time (M=F analysis)

Median HBsAg



Proportion with HBsAg <10 IU/mL



● tobevibart + elebsiran Q4W (N=32) ▲ tobevibart Q2W (N=33)

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

HBsAg, hepatitis B surface antigen; M=F analysis, missing equal failure analysis; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

By Week 96, 4 participants in the tobevibart+elebsiran Q4W cohort and 7 in the tobevibart Q2W cohort had discontinued treatment and are counted as failures in analysis; 1 participant receiving tobevibart Q2W is censored after week 52.

Majority of Adverse Events Through Week 96 were Grade 1 or 2 and Transient

Safety or tolerability measure, n (%) ^a	Tobevibart + elebisan Q4W <i>de novo</i> N = 32	Tobevibart Q2W N = 33
Any TEAE	28 (88)	32 (97)
Grade 1-2	27 (84)	29 (88)
Grade 3	1 (3) ^b	2 (6) ^c
Grade 4	0	1 (3) ^d
Treatment-related TEAE	23 (72)	26 (79)
Treatment-emergent injection site reactions ^e	4 (13)	4 (12)
Treatment-emergent flu-like symptoms ^f	17 (53)	19 (58)
TEAE leading to study drug interruption	0	1 (3) ^g
TEAE leading to study drug discontinuation	0	3 (9) ^h
Serious TEAE	1 (3) ⁱ	1 (3) ^j
Treatment-related serious TEAE	0	0

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.

^aA participant with multiple events within a category is counted only once in that category.

^bGrade 3 worsening of diabetes mellitus type 2 deemed unrelated to study drugs by investigator.

^cGrade 3 hepatocellular carcinoma (SAE) deemed unrelated to study drugs by investigator and grade 3 arterial hypertension deemed related to tobevibart by the investigator.

^dGrade 4 neutropenia on Week 12 and Week 16; recovered to grade 2 or 3 after Week 16 without treatment.

^eInjection-site reactions included pain, pruritus, erythema, swelling.

^fFlu-like symptoms are defined as Influenza like illness or chills or any 2 of headache, myalgia, pyrexia, fatigue, arthralgia reported within 7 days after study dosing.

^gReason for study drug interruption: neutropenia and leukopenia (Preferred term).

^hReason for discontinuation: 2 cases of influenza-like illness (Preferred term) on the day of the first dose and 1 case of hepatocellular carcinoma at day 192.

ⁱOne participant with 2 concurrent SAEs of worsening nasal septum deviation and worsening nasal concha hyperplasia (both Grade 2) who underwent planned admission to the hospital for surgery; both SAEs were deemed unrelated to study drugs by investigator.

^jGrade 3 hepatocellular carcinoma (SAE) at day 192 deemed unrelated to study drugs by investigator

Summary of Key 96 Week Findings

- HDV RNA TND rates increased over time with tobevibart + elebsiran therapy, while rates plateaued with tobevibart monotherapy after week 48
- ALT normalization was similar between tobevibart + elebsiran and tobevibart monotherapy
- Tobevibart + elebsiran therapy rapidly reduced HBsAg to < 10 IU/mL for ~90% of participants
 - In contrast, 25% of participants receiving tobevibart monotherapy achieved HBsAg <10 IU/mL
- Reported adverse events were generally mild to moderate with few study drug-related discontinuations and no related SAEs

In conclusion, at Week 96, tobevibart + elebsiran achieved high rates of HDV RNA TND, reductions in ALT and HBsAg, and was generally well-tolerated

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 (no amplification during RT-PCR).

Tobevibart + elebsiran is now being evaluated in a comprehensive registrational program (ECLIPSE studies)

Acknowledgments

- We thank all study participants, site coordinators, and study investigators
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