Efficacy and safety of tobevibart (VIR-3434) alone or in combination with elebsiran (VIR-2218) in participants with chronic hepatitis delta virus infection: preliminary results from the Phase 2 SOLSTICE trial in non-cirrhotic and compensated cirrhotic participants

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HDV Disease Background

- Chronic hepatitis delta (CHD) causes the most severe form of chronic viral hepatitis leading to high rates of cirrhosis and Hepatocellular carcinoma [1]
- Approximately 12 million people are infected with HDV worldwide [2]
- Approx. 70%-80% of persons with CHD will progress to cirrhosis within 5-10 years [3]
- Given limitations with current treatment options, novel treatments with optimized efficacy, safety and convenience are needed [1, 4-6]

[1] World Health Organization (WHO). July 2023. Hepatitis delta, [2] Asselah T, Rizzetto M. N Eng J Med 2023;389:58-70, [3] Terrault, N, AASLD 2023, [4] European Association for the Study of the Liver (EASL). J Hepatol. 2023;79(2):433-460. doi:10.1016/j.jhep.2023.05.001). [5] Terrault NA, et al. Hepatology. 2018;67(4):1560-1599. doi:10.1002/hep.29800. [6] Lim Y-S, et al. J Hepatol. 2022;77(S1):S69.

CHD, chronic hepatitis D

SOLSTICE Study Background

- The SOLSTICE study is investigating tobevibart (VIR-3434) and elebsiran (VIR-2218) as monotherapy or combination therapy for CHD [1]

- Early data demonstrate potent antiviral activity and no safety signals after 12 weeks of tobevibart + elebsiran combination therapy [2]
  - Median reduction of HDV RNA of of -2.0 log_{10}, and -1.4 log_{10} after Week 12 in tobevibart Q4W and elebsiran Q4W cohorts respectively
  - Median HDV RNA reduction of -4.3 log_{10} (relative to Day 1 of monotherapy) and all participants had HDV RNA < LLOQ after Week 12 in participants who rolled over to tobevibart + elebsiran Q4W

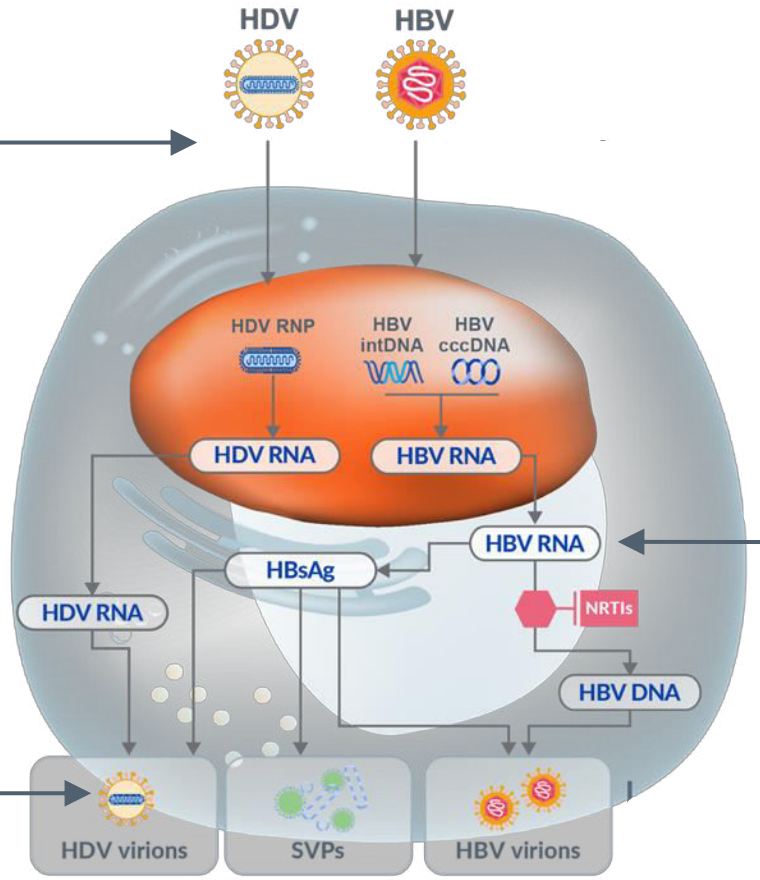
[1] SOLSTICE: NCT05461170. [2] Asselah T, AASLD Nov 2023, Abstract Number: 5004

ALT, alanine aminotransferase; ULN, upper limit of normal; NRTI, nucleoside reverse transcriptase inhibitor; HDV, hepatitis D virus; RNA, ribonucleic acid; HBV, hepatitis B virus; TEAE, Treatment-emergent adverse events; SAE, Serious adverse events, SOLSTICE NCT05461170

Tobevibart and elebsiran Mechanism of Action

Tobevibart (VIR-3434, mAb)

Inhibition of viral entry (neutralization)



Elebsiran (VIR-2218, siRNA)

Reduction of HBsAg RNA (silencing HBV RNA)

Tobevibart

Clearance of free virions (opsonization)

cccDNA, covalently closed circular DNA; DNA, deoxyribonucleic acid; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; int., integrated; mAb, monoclonal antibody; MOA, mechanism of action; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; RNA, ribonucleic acid; RNP, ribonucleoprotein; siRNA, small interfering RNA; SVP, subviral particle.

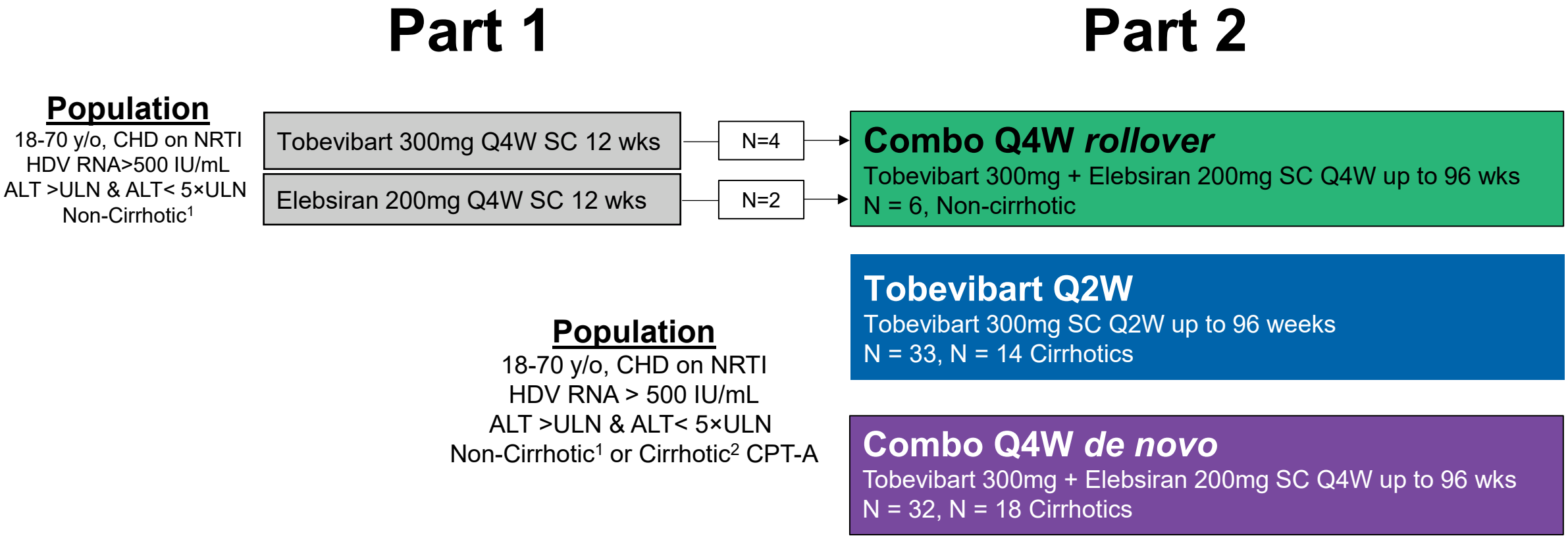
SOLSTICE Study Endpoints

- **Primary Endpoints:**
  - Virologic response and Biochemical response at Week 24
    - Virologic response = HDV RNA < limit of detection (14 IU/mL) or ≥ 2 $\log_{10}$ IU/mL decrease from baseline
    - Biochemical response = ALT < upper limit of normal (F = 33 U/L, M =40 U/L)
  - Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- **Selected Secondary Endpoints:**
  - HDV RNA < LLOQ
  - HDV RNA < LOD
  - HDV TND

[1] Asselah T, AASLD Nov 2023, Abstract Number: 5004

ALT, alanine aminotransferase; ULN, upper limit of normal; NRTI, nucleoside reverse transcriptase inhibitor; HDV, hepatitis D virus; RNA, ribonucleic acid; HBV, hepatitis B virus; TEAE, Treatment-emergent adverse events; SAE, Serious adverse events, SOLSTICE NCT05461170

SOLSTICE Study design



1. Noncirrhotic: Liver biopsy with METAVIR F0-F3 or Liver stiffness < 12 kilopascal (kPa) within 12 months of screening and platelet count > 150×10^3/µL
2. 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 Child-Pugh-Turcotte (CPT) score of 5 or 6, inclusive at screening and at start of study

ALT, alanine aminotransferase; CPT, Child Pugh Turcotte; CHD, Chronic HBsAg, hepatitis B surface antigen; hepatitis delta; HDV, hepatitis D virus; NRTI, nucleoside reverse transcriptase inhibitor; ULN, upper limit of normal; RNA, ribonucleic acid; SC, sub-cutaneous; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SOLSTICE NCT05461170

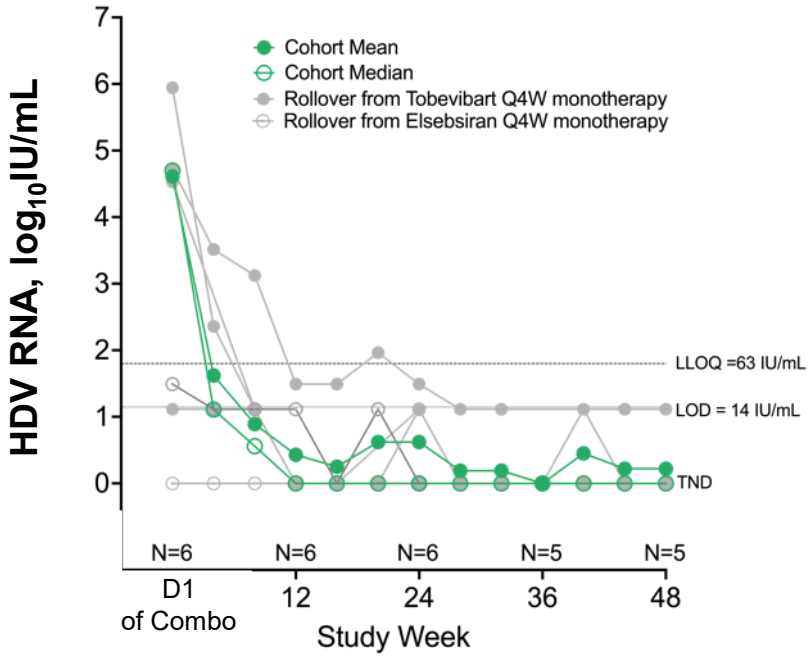
Participant Demographics and Baseline characteristics

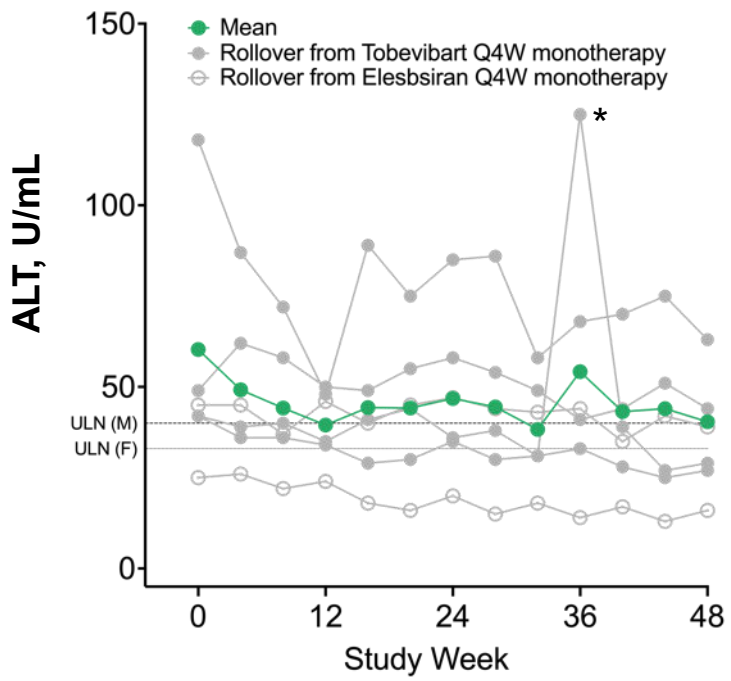
		Combo Q4W *rollover* N = 6[a]	Tobevibart Q2W N = 33	Combo Q4W *de novo* N = 32
Age, y (mean ± SD)		41.0 ± 8.6	44.8 ± 9.2	41.5 ± 8.0
Male, n (%)		4 (66.7)	16 (48.5)	18 (56.3)
Race, n (%)	**White**	6 (100)	28 (84.8)	25 (78.1)
	Black	0 (0)	2 (6.1)	4 (12.5)
	Asian	0 (0)	1 (3.0)	2 (6.3)
HDV RNA[d,e], log_{10} IU/mL (mean ± SD)		Mono[b] 4.6 ± 1.2 Combo[c] 3.0 ± 2.4	5.6 ± 1.1	5.7 ± 1.2
HBsAg[f], log_{10} IU/mL (mean ± SD)		Mono[b] 3.6 ± 1.0 Combo[c] 3.1 ± 1.6	3.7 ± 0.8	3.7 ± 0.6
HBeAg +, n (%)		0	8 (24.2)	3 (9.4)
HBV DNA[g], log_{10} IU/mL, (mean ± SD)		Mono[b] 0.7 ± 0.6	0.7 ± 0.8	0.7 ± 0.7
Cirrhotic participants, n (%)		0	14 (42.4)	18 (56.3)
ALT, U/L (mean ± SD)		Mono[b] 60.3 ± 19.6 Combo[c] 55.2 ± 36.2	75.7 ± 58.8	83.4 ± 47.1
Platelets, 10^9/L (mean ± SD)		316.8 ± 184.1	200.2 ± 74.5	189.4 ± 58.0
Liver stiffness kPa (mean ± SD)		8.0 ± 3.2	13.5 ± 8.7	13.6 ± 7.4
FibroTest Score (mean ± SD)		0.47 ± 0.25	0.45 ± 0.23	0.48 ± 0.25

[a] Data includes participants who have completed at least 24 weeks of Combination therapy
[b] Data refers to Day 1 of monotherapy period
[c] Data refers to Day 1 of Combo Q4W period
[d] Robogene® 2.0 Assay, supplied and analyzed by Viroclinics-DDL™
[e] HDV genotypes are pending
[f] Roche's Elecsys® II Quant II, supplied and analyzed by PPD™
[g] Cobas HBV Qualitative nucleic acid test

ALT, alanine aminotransferase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis e antigen; HDV, hepatitis D virus; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RNA, ribonucleic acid; SD, Standard Deviation; ULN, upper limit of normal;

Tobevibart+elebsiran (Combo *rollover*) cohort: Virologic and Biochemical Responses





*One participant experienced elevated ALT 125 IU/mL & AST 311 IU/mL, other liver function tests were within normal limits, HDV RNA was <LOD, and HBsAg = 1.3 IU/mL. The PI attributed the rise in ALT and AST, with an abrupt increase in physical activity.

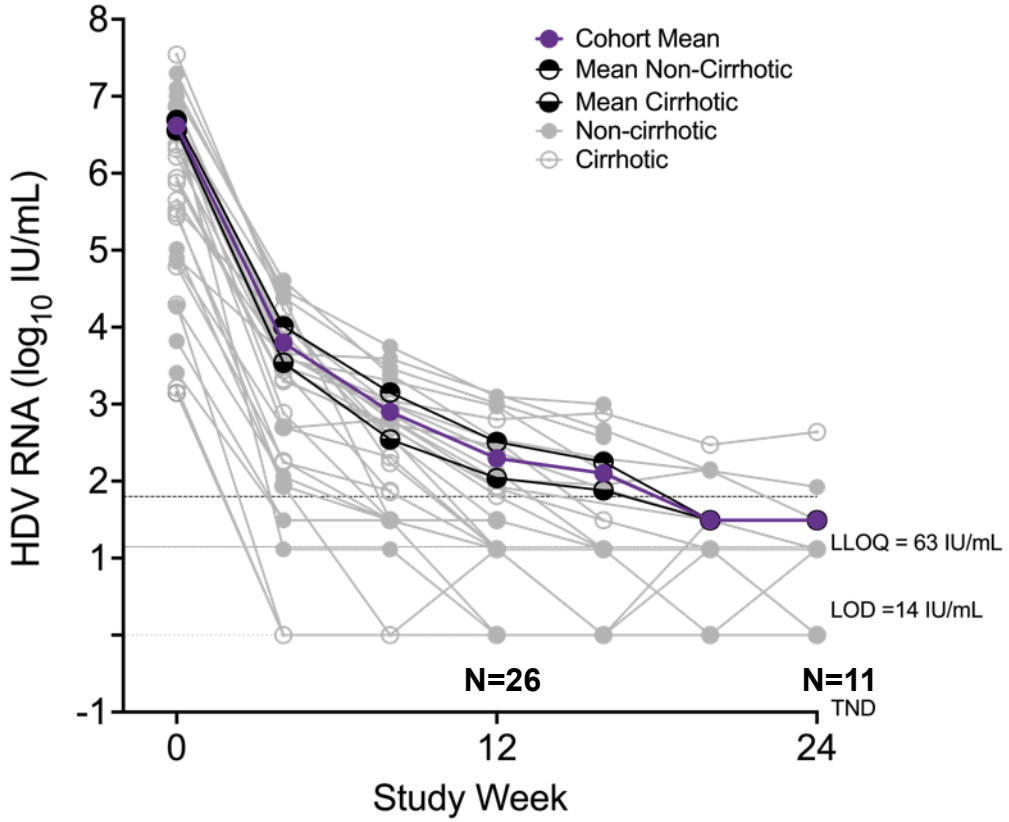
	Combo Q4W *rollover*		
	Wk 12 N=6[a]	Wk 24 N=6[a]	Wk 48 N=5[a]
HDV RNA < LLOQ, n (%)	6 (100)	6 (100)	5 (100)
HDV RNA < LOD, n (%)	5 (83.3)	5 (83.3)	5 (100)
HDV RNA TND, n (%)	4 (66.7)	3 (50)	4 (80)
ALT normalization, n (%)	2 (33.3)	2 (33.3)	2 (40)

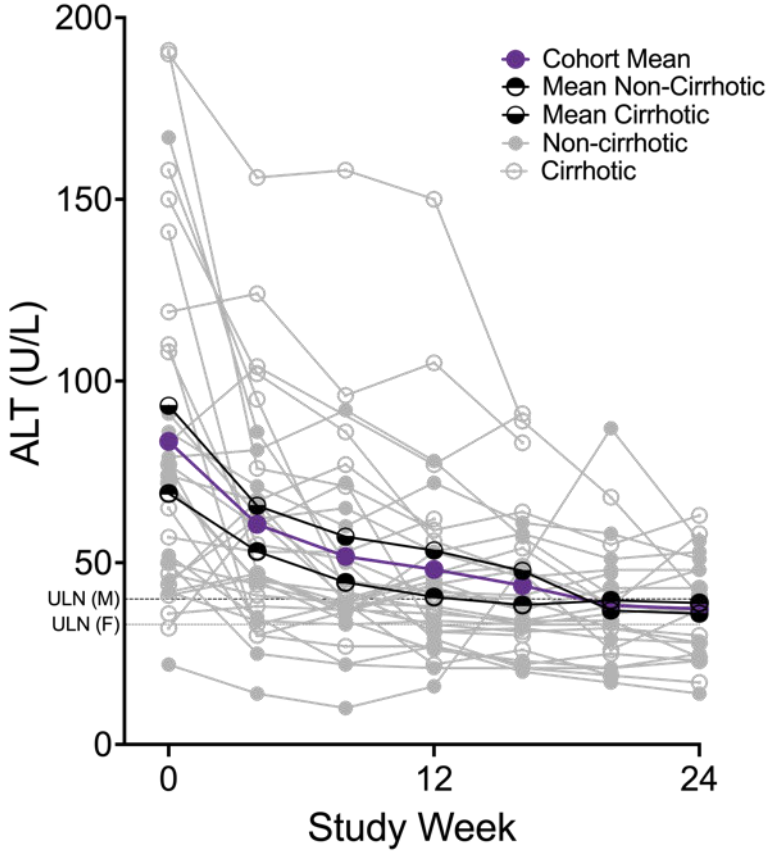
[a] N is the number of participants who have completed the study visit

The 6th participant has completed 40 weeks of Combo therapy and has HDV RNA TND and ALT <ULN

Robogene® 2.0 Assay was used to assess HDV RNA, analyzed by Viroclinics-DDL™; LOD, limit of detection (values < LOD are plotted as 13 IU/mL); LLOQ, lower limit of quantification (values < LLOQ and > LOD are plotted as 31 IU/mL); TND, Target Not Detected (TND is plotted as 0 IU/mL); ALT, Alanine Aminotransferase; HDV, hepatitis D virus; RNA, ribonucleic acid; ULN, upper limit of normal; ULN M = 40 IU/mL, ULN F = 33 IU/mL

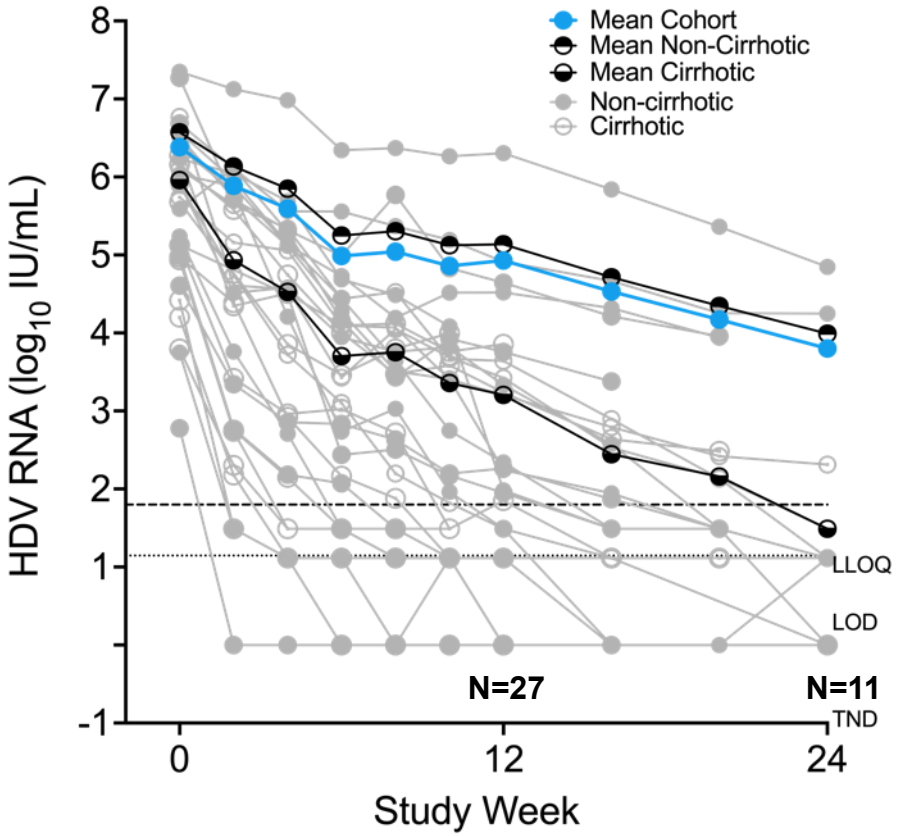
tobevibart + elebsiran (Combo *de novo*) cohort: Virologic and Biochemical Responses

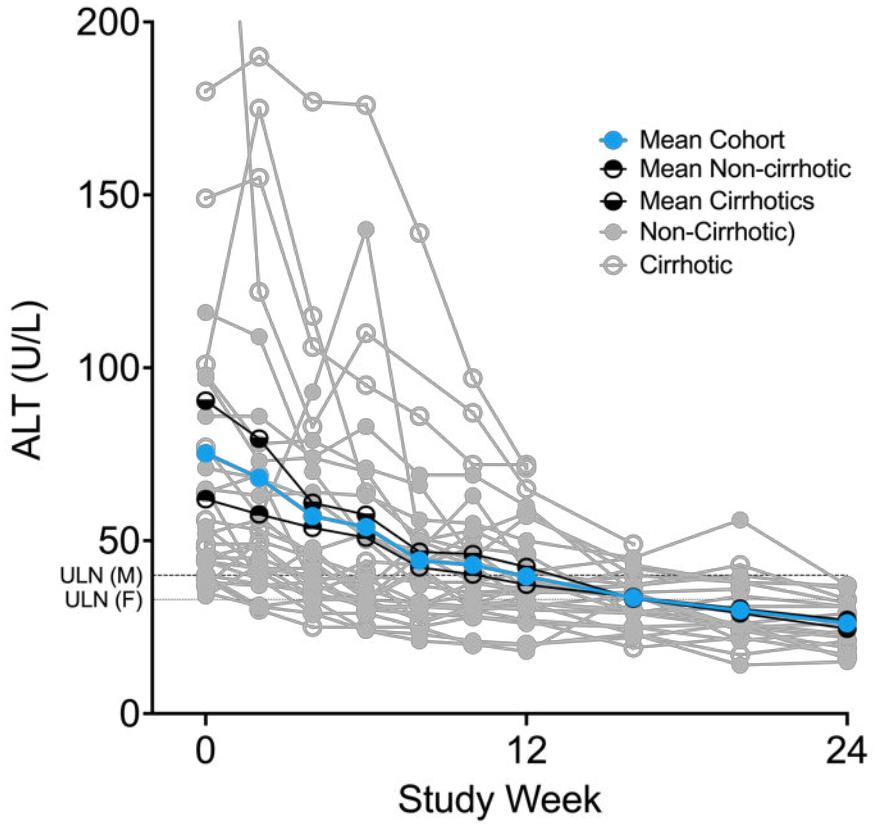




Robogene® 2.0 Assay was used to assess HDV RNA, analyzed by Viroclinics-DDL™; LOD, limit of detection (values < LOD are plotted as 13 IU/mL); LLOQ, lower limit of quantification (values < LLOQ and > LOD are plotted as 31 IU/mL); ALT, Alanine Aminotransferase; HDV, hepatitis D virus; RNA, ribonucleic acid; SD, Standard Deviation; ULN, upper limit of normal; ULN M = 40 IU/mL, ULN F = 33 IU/mL

tobevibart Q4W cohort: Virologic and Biochemical Responses





Robogene® 2.0 Assay was used to assess HDV RNA, analyzed by Viroclinics-DDL™; LOD, limit of detection (values < LOD are plotted as 13 IU/mL); LLOQ, lower limit of quantification (values < LLOQ and > LOD are plotted as 31 IU/mL); ALT, Alanine Aminotransferase; HDV, hepatitis D virus; RNA, ribonucleic acid; SD, Standard Deviation; ULN, upper limit of normal; ULN M = 40 IU/mL, ULN F = 33 IU/mL

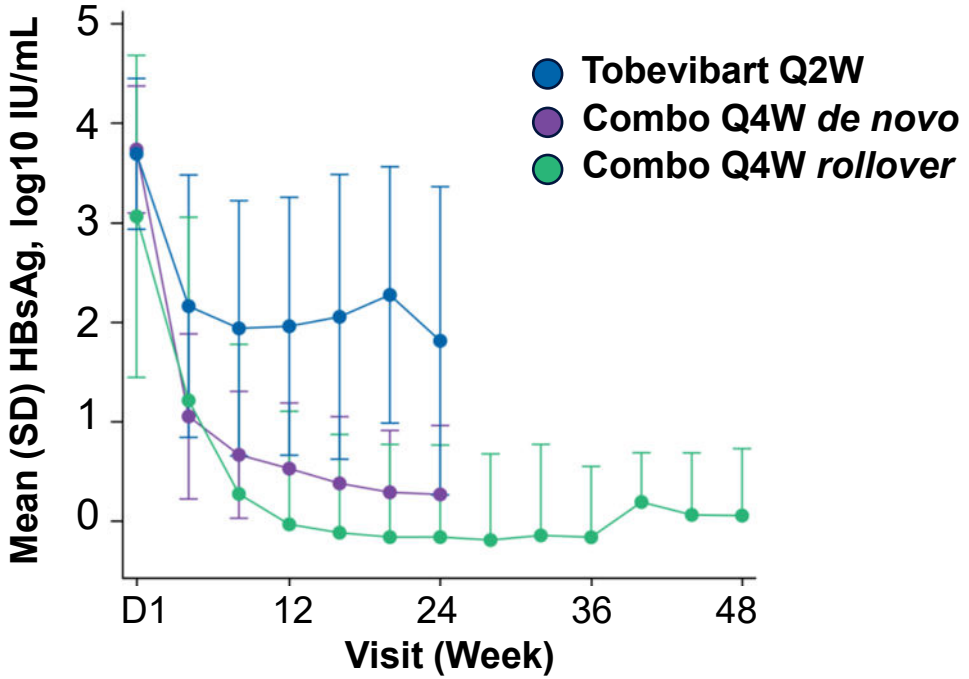
Tobevibart Q2W and tobevibart + elebsiran (Combo *de novo*) cohort: Virologic and Biochemical Responses

	Tobevibart Q2W		Combo Q4W *de novo*	
	Week 12 N=26[a]	Week 24 N=11[a]	Week 12 N=27[a]	Week 24 N=11[a]
HDV RNA < LLOQ, n (%)	7 (26.9)	6 (54.5)	14 (51.9)	11 (100)
HDV RNA < LOD, n (%)	5 (19.2)	5 (45.5)	10 (37)	10 (90.9)
HDV RNA TND, n (%)	2 (7.7)	2 (18.2)	4 (14.8)	6 (54.5)
ALT normalization, n (%)	14 (53.8)	7 (63.6)	12 (44.4)	7 (63.6)

[a] N is the number of participants who have completed the study visit or discontinued before the study visit

Robogene® 2.0 Assay was used to assess HDV RNA, analyzed by Viroclinics-DDL™; LOD, limit of detection (values < LOD are plotted as 13 IU/mL); LLOQ, lower limit of quantification (values < LLOQ and > LOD are plotted as 31 IU/mL); ALT, Alanine Aminotransferase; HDV, hepatitis D virus; RNA, ribonucleic acid; SD, Standard Deviation; ULN, upper limit of normal; ULN M = 40 IU/mL, ULN F = 33 IU/mL

Tobevibart Q2W and tobevibart + elebsiran (Combo) cohorts: HBsAg Response Responses



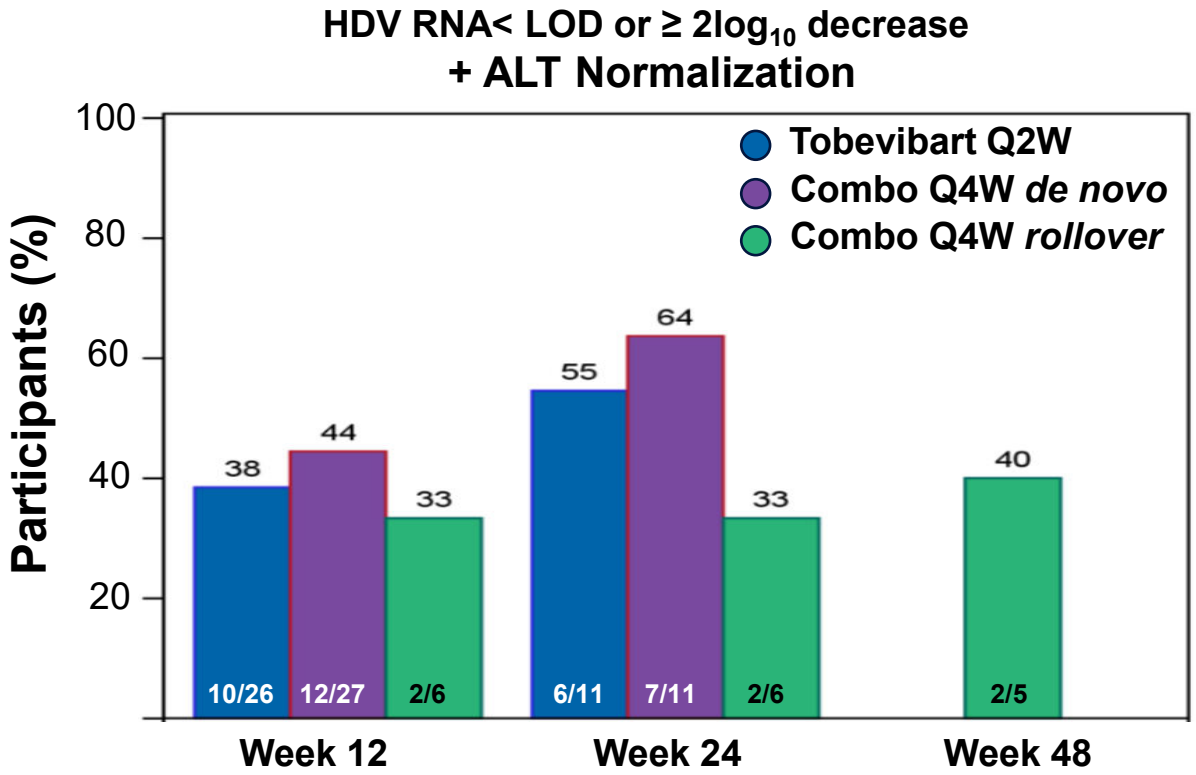
	Tobevibart Q2W		Combo Q4W *de novo*		Combo Q4W *rollover*		
	Wk 12 N=25[a]	Wk 24 N=9[a]	Wk 12 N=29[a]	Wk 24 N=14[a]	Wk 12 N=6[a]	Wk 24 N=6[a]	Wk 48 N=5[a]
Δ HBsAg relative to Day 1 (Mean ± SD)[b], log_{10} IU/mL	-1.7 ± 0.8	-1.8 ± 0.9	-3.2 ± 0.5	-3.3 ± 0.5	-3.1 ± 1.0	-3.2 ± 0.9	-3.5 ± 0.8

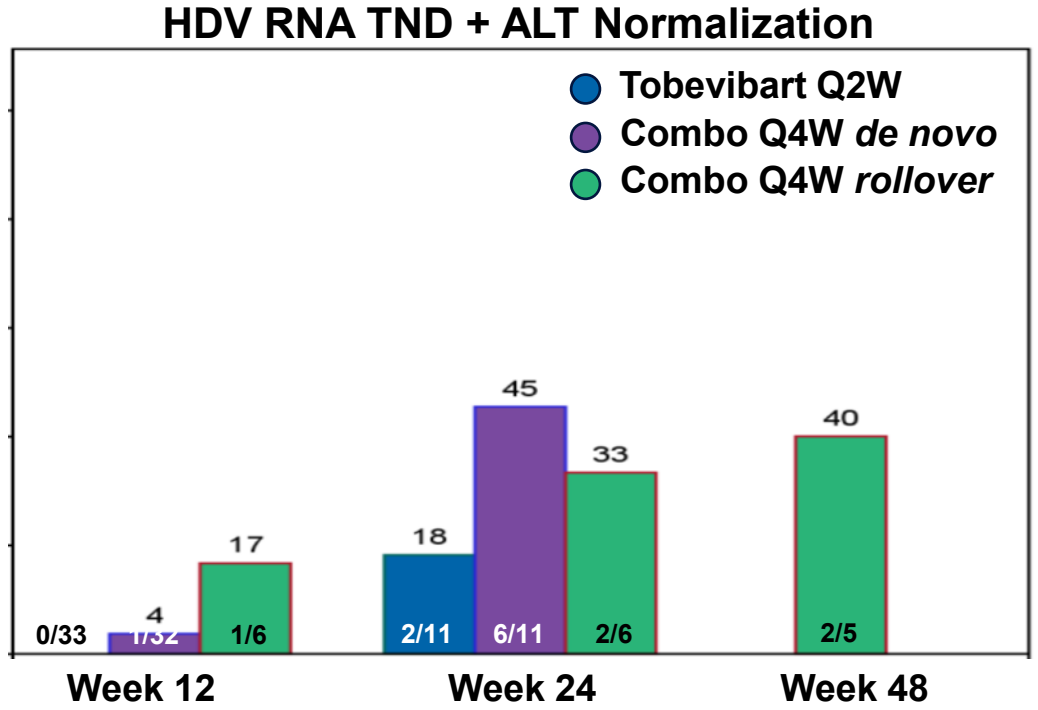
[a] N is the number of participants who have completed the study visit or discontinued before the study visit

[b] For Combo Q4W *rollover* Day 1 = Day 1 of Combination therapy

HBsAg, hepatitis B virus surface antigen; SD, Standard Deviation; Q4W, every 4 weeks; Q2W, every 2 weeks.

Preliminary Combined response rates





Robogene® 2.0 Assay was used to assess HDV RNA, analyzed by Viroclinics-DDL™; LOD, limit of detection (14 IU/mL); LLOQ, lower limit of quantification (63 IU/mL); ALT, Alanine Aminotransferase; HDV, hepatitis D virus; RNA, ribonucleic acid; ALT ULN M = 40 IU/mL, ALT F = 33 IU/mL

Cumulative Summary Safety and Tolerability

Participants with	Combo Q4W *rollover* *(up to WK48)* n = 6	Tobevibart Q2W (up to WK24) n = 33	Combo Q4W *de novo* (up to WK24) n = 32
Any TEAE, n (%)	4 (66.7)	29 (87.9)	25 (78.1)
TEAE by maximum severity grade, n (%) Grade 1 Grade 2 Grade ≥3	 0 (0) 4(66.7) 0 (0)	 11 (33.3) 17 (51.5) 1 (3.0)	 9 (28.1) 16 (50.0) 0 (0)
Related TEAE, n (%)[a]	2 (33)[d]	26 (78.8)[b]	22 (68.8)[c]
Any Injection site reactions, n (%)	0 (0)	1 (3)	2 (6.3)
Serious AE n (%)	0 (0)	0 (0)	1 (3)[f]
AE leading to treatment discontinuation, n (%)	0 (0)	2 (6)	0 (0)
AE leading to death, n (%)	0 (0)	0 (0)	0 (0)

Most TEAE were Grade 1-2, with very few serious TEAE and no deaths. TEAEs led to treatment discontinuation in 2 participants
The majority of the Influenza-like illness, chills, arthralgias, myalgias and pyrexia TEAE are reported within 24 hours of the first dose and resolve within 48 hours

[a] PT: Neutropenia, Leukopenia
[b] Influenza like Illness (n=7), Pyrexia (n=6), Chills (n=3), Myalgia (n=6), Dizziness (n=4), Nausea (n=4), Headache (n=2), Asthenia (n=2), Fatigue (n=2), Arthralgia (n=2), Back Pain (n=1), Vomiting (n=2), Rhinitis (n=1), Leukopenia (n=1), Neutropenia (n=1), Erythema (n=1)
[c] Influenza like Illness (n=8), Pyrexia (n=6), Chills (n=6), Headache (n=4), Dizziness (n=1), Arthralgia (n=1), Nausea (n=1), Vomiting (n=1), Rhinitis (n=1)
[d] Arthralgia (n=2), Headache (n=2), Chills (n=1)
[f] SAE, unrelated (partner pregnancy resulting in miscarriage)

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D virus; RNA; ISR, injection site reactions; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TEAE, treatment emergent adverse events; NA, not applicable

Summary

- **With tobevibart monotherapy and tobevibart with elebsiran combination therapy**
  - High virologic responses were observed in both cohorts at Week 24
  - ALT normalization rates were similar in both cohorts at Week 24
  - Combined endpoint responses at Week 24 were high and increased over time
- **More rapid declines in HDV RNA was observed in participants receiving tobevibart with elebsiran combination therapy**
- **Virologic responses were maintained through Week 48 in the tobevibart with elebsiran *rollover* cohort**
- **The majority of AEs were Gr 1-2 and transient**
- **No ALT flares were observed in tobevibart monotherapy or combination therapy cohorts**
- **Based on preliminary findings, participants receiving tobevibart alone or in combination with elebsiran demonstrate rapid Virologic responses with improvement in** ALT normalization **over time**
- **AEs were low-grade, transient, and resulted in low discontinuation rates**

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; IU, international unit; AE, adverse events; SAE, serious adverse event; siRNA, small interfering ribonucleic acid;

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