Poster WED-389

Pharmacokinetics and Safety of Single Dose of the Monoclonal Antibody Tobevibart (VIR-3434) Administered as Monotherapy or in Combination with the Small Interfering RNA Elebsiran (VIR-2218) in Cirrhotic Participants with Mild Hepatic Impairment

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Background

- Tobevibart (VIR-3434) is an investigational human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to the antigenic loop present in all forms of hepatitis B surface antigen (HBsAg).
- Elebsiran (VIR-2218) is a N-acetylgalactosamine (GalNAc)–conjugated, double-stranded RNA interference (RNAi) investigational therapeutic that targets the X region of the hepatitis B virus (HBV) genome that is common to all HBV viral RNA transcripts.
- The GalNAc moiety enables targeted delivery of elebsiran into the liver via uptake by asialoglycoprotein receptors (ASGPR) expressed primarily and abundantly on the surface of hepatocytes.[1]
- Both tobevibart and elebsiran are in clinical development for the treatment of chronic hepatitis B virus (HBV) infection and hepatitis D virus (HDV) infection.
  - In participants with chronic HBV infection, tobevibart 300 mg and elebsiran 200 mg administered subcutaneously (SC) in combination achieved the largest HBsAg reductions at nadir and sustained HBsAg reduction[2,3].
  - Similarly, in participants with chronic HDV infection, at week 12, potent antiviral activity with up to -4.3 log decline in plasma HDV RNA was observed with the combination in the Phase 2 SOLSTICE study.[4]
- We have previously demonstrated that a dose of elebsiran 200mg SC was generally well tolerated in participants with CPT-B HI. While elebsiran exposures were higher in participants with CPT-B HI, increase in exposure was not considered clinically relevant and did not warrant any dose adjustment.[5]

Objective

- To assess the single dose pharmacokinetics (PK) and safety of tobevibart administered as monotherapy or in combination with elebsiran in participants with cirrhosis and mild hepatic impairment (HI) with a Child-Pugh-Turcotte Class-A (CPT-A) score, and in matched healthy volunteer participants (HV).

Methods

- VIR-2218-V107 (NCT05484206) is a Phase 1, open-label, single-dose parallel-group study.
- Participants with HI and the HV were matched (1:1) by sex, age (± 10 years), and body mass index (BMI) (± 20%) at screening.
- Key eligibility criteria:
  - Age ≥ 18 to ≤ 70 years
  - BMI ≥ 18.5 to ≤ 40 kg/m^2
  - eGFR ≥ 60 mL/min/1.73m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) equation
  - Liver cirrhosis as defined by either a historical (a) liver biopsy with METAVIR F4 or (b) liver elastography with liver stiffness ≥ 12.5 kilopascal (kPa) within 12 months of screening or (c) liver elastography with liver stiffness ≥ 12.5 kPa in the screening window. CPT score 5 or 6 for mild HI (CPT-A) at screening
- Participants received a single SC dose of tobevibart 300 mg or tobevibart 300 mg + elebsiran 200 mg. Blood samples were collected up to 18 weeks post-dose to measure the concentrations of tobevibart, elebsiran and its major metabolite, AS(N-1)3'VIR-2218. Urine samples were collected over 72 hours post-dose to measure the concentrations of elebsiran and its major metabolite, AS(N-1)3'VIR-2218.
  - Concentrations of tobevibart in human serum were determined using a validated electrochemiluminescence quantitative method on the MesoScale Discovery (Rockville, MD) platform with a lower limit of quantitation of 10 ng/mL.
  - Concentrations of elebsiran and its major metabolite in K_2EDTA plasma and urine measured using validated liquid chromatography–time-of-flight mass spectrometry methods with lower limit of quantitation of 10 ng/mL in plasma and urine.
  - PK parameters were estimated using non-compartmental analysis in WinNonlin® (Certara LP, Princeton, NJ) and summarized using descriptive statistics.
- Adverse event (AE) monitoring, clinical laboratory, physical examinations, and electrocardiographic evaluations were performed throughout the study.

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Results

Participants Characteristics

- Eight (8) participants with cirrhosis and CPT-A HI and 8 HV were enrolled for each cohort of tobevibart monotherapy and tobevibart + elebsiran combination therapy.
- The baseline demographics and other selected clinical characteristics of the participants are shown in **Table 1**.

Table 1. Demographics and Clinical Characteristics

	Tobevibart Monotherapy		Tobevibart + Elebsiran Combination Therapy	
Cohort Liver Status	CPT-A	HV	CPT-A	HV
N	8	8	8	8
Male, n (%)	4 (50.0)	4 (50.0)	6 (75.0)	6 (75.0)
Age (years), median (min, max)	57.5 (50, 62)	56.5 (43, 62)	59.5 (53, 70)	56.5 (48, 63)
White, n (%)	8 (100)	6 (75.0)	8 (100)	6 (75.0)
Ethnicity, n (%)				
Hispanic or Latino	7 (87.5)	5 (62.5)	7 (87.5)	6 (75.0)
Not Hispanic or Latino	1 (12.5)	3 (37.5)	1 (12.5)	2 (25.0)
BMI (kg/m^2), median (min, max)	36.4 (23, 40)	31.6 (26, 37)	34.3 (27, 40)	31.1 (27, 38)
eGFR (mL/min/1.73m^2), median (min, max)	95.92 (56.7, 124.1)	80.78 (67.5, 87.2)	91.84 (67.2, 143.2)	94.86 (70.9, 127.8)
CPT Score, median (min, max)	5.0 (5, 6)	NA	5.0 (5, 6)	NA

CPT, Child-Pugh-Turcotte; eGFR, Estimated glomerular filtration rate; HI, Hepatic impairment participant; HV, healthy volunteer participants.

Pharmacokinetics of Tobevibart

- Tobevibart PK exposure was comparable in participants with CPT-A and HV (**Figure 1**).
  - In tobevibart monotherapy cohort, geometric mean ratios (GMR) of tobevibart C_{max}, AUC_{last} and AUC_{inf} in participants with CPT-A compared to HV were 0.87–0.96 (**Table 2**), indicating no significant impact of hepatic impairment on exposure of tobevibart relative to healthy volunteers.
  - In tobevibart + elebsiran combination therapy cohort, GMR of tobevibart C_{max}, AUC_{last} and AUC_{inf} in participants with CPT-A compared to HV were 1.00–1.06 (**Table 2**), also indicating no significant impact of hepatic impairment on exposure of tobevibart relative to healthy volunteers.
- Tobevibart PK was similar in monotherapy and combination therapy in both participants with CPT-A and HV, indicating no PK drug-drug interaction (DDI) between tobevibart and elebsiran.

Figure 1. Tobevibart Serum Concentration Profiles in Participants with CPT-A and HV Following Single Subcutaneous Dose of A) Tobevibart 300 mg and B) Tobevibart 300 mg + Elebsiran 200 mg

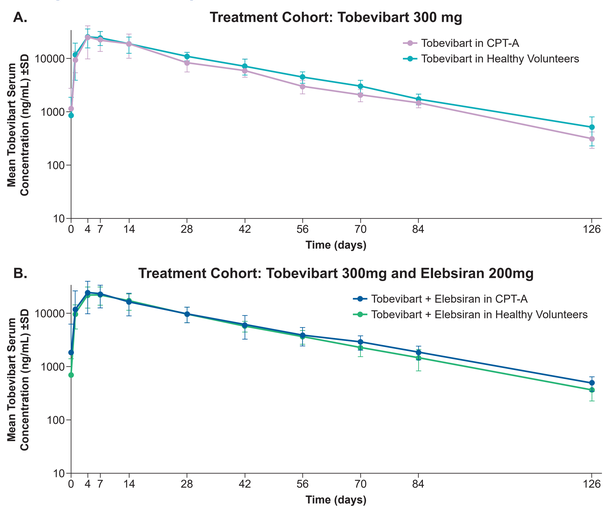


Table 2. PK Parameters for Tobevibart Following Single Subcutaneous Dose of Tobevibart 300 mg or Tobevibart 300 mg + Elebsiran 200 mg

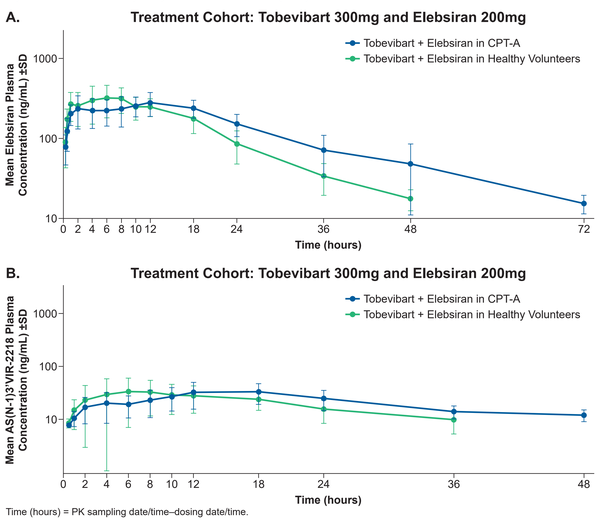
	Tobevibart Monotherapy		Tobevibart + Elebsiran Combination Therapy	
Cohort Liver Status	CPT-A	HV	CPT-A	HV
AUC_{last} (day*ng/mL)	675,000 (33.2)	775,000 (19.0)	696,000 (40.0)	695,000 (21.9)
AUC_{inf} (day*ng/mL)	684,000 (33.1)	783,000 (20.5)	713,000 (39.5)	706,000 (21.7)
C_{max} (ng/mL)	24,600 (56.7)	25,700 (36.6)	23,900 (61.0)	22,600 (33.6)
T_{max} (day)	5.54 (3.90, 14.1)	4.02 (3.99, 7.00)	5.48 (1.01, 13.9)	6.42 (4.00, 13.1)
T_{last} (day)	126 (119, 133)	127 (36.0, 134)	126 (124, 128)	126 (123, 127)
CL/F (mL/day)	438 (33.1)	383 (20.5)	421 (39.5)	425 (21.7)
V_z/F (L)	12.5 (32.1)	11.8 (27.4)	13.5 (43.3)	12.4 (34.7)
$t_{1/2}$ (day)	19.4 (16.4, 25.2)	20.7 (18.6, 29.7)	22.6 (19.2, 26.8)	21.2 (13.8, 25.6)
	Geometric Mean Ratio (90% CI) CPT-A vs HV			
C_{max}	0.957 (0.64, 1.42)		1.058 (0.71, 1.59)	
AUC_{last}	0.871 (0.69, 1.10)		1.002 (0.76, 1.32)	
AUC_{inf}	0.874 (0.68, 1.12)		1.009 (0.77, 1.32)	

Median (minimum, maximum) are reported for T_{max}, T_{last} and $t_{1/2}$; geometric mean (geometric CV%) are reported for the other PK parameters.
AUC, area under curve; AUC_{last}, AUC to last measurable concentration; CL/F, apparent clearance; C_{max}, maximum concentration; T_{last}, time of last measurable concentration; T_{max}, time to reach C_{max}; $t_{1/2}$, half-life; V/F, apparent volume of distribution.

Pharmacokinetics of Elebsiran and its Major Metabolite AS(N-1)3'VIR-2218

- Exposure of elebsiran was comparable in participants with CPT-A and HV (**Figure 2A**). GMR of C_{max}, AUC_{last} and AUC_{inf} in CPT-A to HV were 0.83–1.25 indicating no significant impact of hepatic impairment on exposure of elebsiran relative to healthy volunteers.
- Similar metabolite PK exposure was observed in participants with CPT-A compared to HV (**Figure 2B**). GMR of C_{max}, AUC_{last} and AUC_{inf} of in participants with CPT-A vs. HV were 0.98–1.48 (**Table 3**).
- The percentage of drug excreted in urine (%fe) was similar in CPT-A participants compared to HV with 18.2% versus 14.8% (**Table 3**).

Figure 2. Plasma Concentration Profiles Following Single Subcutaneous Dose of Tobevibart 300 mg + Elebsiran 200 mg in Participants with CPT-A and HV for A) Elebsiran and B) Major Metabolite AS(N-1)3'VIR-2218



Time (hours) = PK sampling date/time–dosing date/time.

Table 3. PK Parameters for Elebsiran and AS(N-1)3'VIR-2218 Following Single Subcutaneous Dose of Tobevibart 300 mg + Elebsiran 200 mg

	Elebsiran		AS(N-1)3'VIR-2218	
Cohort Liver Status	CPT-A	HV	CPT-A	HV
AUC_{last} (h*ng/mL)	7,290 (26.8)	5,810 (22.4)	857 (37.8)	579 (58.4)
AUC_{inf} (h*ng/mL)	7,660 (25.0)	6,130 (23.6)	1,190 (NA)	1,020 (NA)
C_{max} (ng/mL)	278 (36.1)	337 (37.0)	32.3 (49.9)	33.0 (62.0)
T_{max} (h)	10.0 (2.00, 12.0)	7.00 (1.00, 8.05)	18.0 (12.0, 23.6)	9.03 (4.00, 18.0)
T_{last} (h)	48.1 (36.0, 72.0)	36.0 (24.0, 48.4)	36.0 (35.7, 48.1)	24.3 (18.0, 36.0)
CL/F (L/h)	26.1 (25.0)	32.6 (23.6)		
V_z/F (L)	353 (53.3)	327 (57.8)		
$t_{1/2}$ (h)	8.61 (6.55, 18.6)	7.28 (3.05, 10.7)	11.4 (8.03, 14.9)	8.01 (5.02, 11.0)
% fe	18.2 (29.7)	14.8 (32.4)	2.93 (31.7)	1.94 (44.3)
	Geometric Mean Ratio (90% CI) CPT-A vs HV			
C_{max}	0.826 (0.60, 1.14)		0.978 (0.60, 1.59)	
AUC_{last}	1.254 (1.00, 1.56)		1.482 (0.96, 2.28)	
AUC_{inf}	1.249 (0.99, 1.57)		1.165 (0.77, 1.76)	

Median (minimum, maximum) are reported for T_{max}, T_{last} and $t_{1/2}$; geometric mean (geometric CV%) are reported for the other PK parameters.
AUC, area under curve; AUC_{last}, AUC to last measurable concentration; CL/F, apparent clearance; C_{max}, maximum concentration; T_{last}, time of last measurable concentration; T_{max}, time to reach C_{max}; $t_{1/2}$, half-life; V/F, apparent volume of distribution, % fe, percentage of drug excreted in urine.

Safety and Tolerability

- In tobevibart monotherapy cohort, there was a total of 14 adverse events (AE), out of which 9 AEs were observed in participants with CPT-A HI and 5 in HV. Most of the events were unrelated to the study drugs except for extremity pain and lower abdominal pain that were observed in a participant with CPT-A and assessed as related to tobevibart. These 2 events were not serious and recovered with no sequelae. One unrelated SAE of Grade 2 asthma exacerbation was reported in a participant with CPT-A HI with a prior history of asthma that resolved with no sequelae.
- In the tobevibart and elebsiran combination therapy cohort, a total of 5 events were reported, out of which 4 AEs were observed in participants with CPT-A HI and 1 in HV. All the events were unrelated to the study drugs, were not serious and recovered with no sequelae.

Conclusions

- A single subcutaneous dose of tobevibart 300 mg monotherapy and tobevibart 300 mg SC + elebsiran 200 mg SC combination therapy was well tolerated in CPT-A HI participants and no drug related SAE was observed.
- Tobevibart and elebsiran exposures were comparable in participants with CPT-A versus matched HV.
- Based on collective PK and safety data, no dose adjustment is warranted for tobevibart and elebsiran in participants with CPT-A HI.
- Data supports continued evaluation of the tobevibart 300 mg monotherapy and tobevibart 300 mg + elebsiran 200 mg combination therapy in patients with HBV and HDV infection with up to CPT-A hepatic impairment.
- Based on these data, tobevibart 300 mg monotherapy and tobevibart 300 mg + elebsiran 200 mg combination therapy are currently being evaluated in participants with CPT-A HI and HDV infection as chronic therapy (SOLSTICE Phase 2 trial; EASL Congress 2024 presentation No. OS-127; ClinicalTrials.gov Identifier: NCT05461170).

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