Single-dose pharmacokinetics of VIR-3434, a novel neutralizing monoclonal antibody, in participants with chronic hepatitis B virus infection

Poster SAT-177

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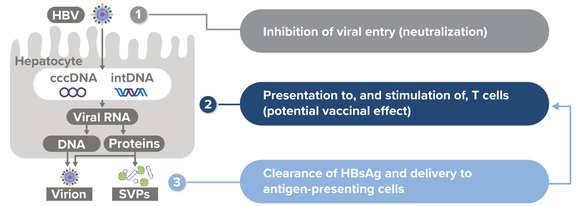
Background

- Chronic hepatitis B virus (HBV) infection is a major global public health issue affecting approximately 300 million people worldwide[1]
- VIR-3434 is an investigational monoclonal antibody, targeting the antigenic loop of the hepatitis B surface antigen (HBsAg)
- VIR-3434 is currently in clinical development for the treatment of chronic HBV and hepatitis D virus (HDV) infection and has multiple potential modes of action (**Figure 1**)

Figure 1. VIR-3434 Has Multiple Potential Modes of Action



cccDNA, covalently closed circular DNA; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; intDNA, integrated DNA; RNA, ribonucleic acid; SVPs, subviral particles.

- In healthy participants, VIR-3434 is associated with favorable safety and pharmacokinetic (PK) profiles.[2] VIR-3434 exhibited linear PK at single subcutaneous (SC) doses of 90 mg to 900 mg, with median time to maximum concentration (C_{max}) of 3–7 days and median terminal half-life ($t_{1/2}$) of approximately 25 days
- VIR-3434 is well tolerated in participants with chronic HBV infection.[3,4] We have previously demonstrated that a single dose of VIR-3434 was associated with rapid reductions in HBsAg in most participants; however, reductions were of shorter duration in those with HBsAg > 3,000 IU/mL at baseline versus those with HBsAg ≤ 3,000 IU/mL
  - Participants who received VIR-3434 300 mg achieved the largest HBsAg reduction at nadir (day 4–11) and sustained HBsAg reduction at week 4, regardless of baseline HBsAg
- Here we report, for the first time, the free VIR-3434 PK after single-dose administration in participants with chronic HBV infection

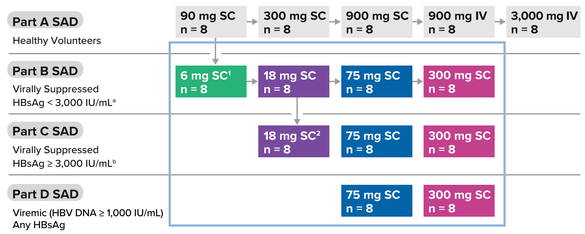
Study Objective

- To evaluate the safety, tolerability, and antiviral activity of VIR-3434, and characterize the serum PK profile of VIR-3434 after a single dose, in participants with chronic HBV infection

Methods

- VIR-3434-1002 is a phase 1 randomized, double-blind, placebo-controlled, single ascending dose (SAD) study (**Figure 2**)

Figure 2. Study Design



[a]Cohort 1b (6 mg SC) enrolled participants with screening HBsAg <1,000 IU/mL.
[b]Cohort 1c (18 mg SC) enrolled participants with any screening HBsAg.
HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IV, intravenous; SAD, single ascending dose; SC, subcutaneous.

- Eligible participants were noncirrhotic adults (≥ 18 years old) with chronic HBV infection
- 8 participants per cohort were randomly assigned 6:2 to receive a single dose of VIR-3434 or placebo by SC injection
- Serum PK samples were collected over 24 hours (day 1), and on days 3, 7, 10, 14, and weeks 4, 8, 12, 16, 24, 32, and 40:
  - Concentrations of free VIR-3434 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
  - PK parameters were estimated using standard noncompartmental methods in WinNonlin®, V8.3 (Certara L.P., Princeton, NJ) and summarized using descriptive statistics
  - Correlation between PK parameters (AUC_{last}, C_{max}) and baseline HBsAg were reported using a linear regression model and Pearson correlation coefficient

Results

Participants Characteristics

- 72 participants were enrolled in Parts B–D; 54 participants received VIR-3434 SC
- Overall, demographic and baseline characteristics were balanced across all cohorts
- Most participants were men and Asian or White; age ranged from 31–64 years across cohorts, and about 50% of participants had a baseline HBsAg of 3,000 IU/mL or lower

Table 1. Demographics and Baseline Characteristics

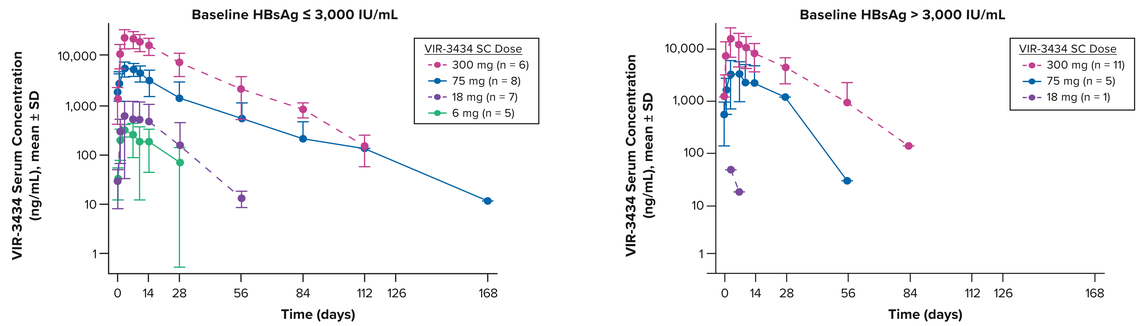
Parameter	Part B				Part C			Part D	
	VIR-3434 6 mg n = 6	VIR-3434 18 mg n = 6	VIR-3434 75 mg n = 6	VIR-3434 300 mg n = 6	VIR-3434 18 mg n = 6	VIR-3434 75 mg n = 6	VIR-3434 300 mg n = 6	VIR-3434 75 mg n = 6	VIR-3434 300 mg n = 6
Age, (y), mean (SD)	56.3 (5.72)	49.0 (6.93)	50.8 (8.35)	50.0 (8.81)	44.5 (10.82)	38.2 (8.33)	38.8 (8.95)	42.7 (7.71)	38.0 (6.16)
Sex, n (%)									
Men	6 (100)	6 (100)	4 (66.7)	5 (83.3)	3 (50.0)	4 (66.7)	4 (66.7)	2 (33.3)	3 (50.0)
Women	0	0	2 (33.3)	1 (16.7)	3 (50.0)	2 (33.3)	2 (33.3)	4 (66.7)	3 (50.0)
Race/ethnicity, n (%)									
White	3 (50.0)	3 (50.0)	2 (33.3)	1 (16.7)	1 (16.7)	5 (83.3)	6 (100)	0	3 (50.0)
Black	0	1 (16.7)	0	1 (16.7)	0	1 (16.7)	0	0	1 (16.7)
Asian	3 (50.0)	2 (33.3)	4 (66.7)	4 (66.7)	5 (83.3)	0	0	5 (83.3)	2 (33.3)
Other	0	0	0	0	0	0	0	1 (16.7)	0
BMI (kg/m^2), mean (SD)	25.4 (1.52)	25.9 (3.99)	24.4 (2.21)	27.3 (3.04)	24.9 (4.85)	25.4 (2.21)	24.8 (3.29)	24.5 (3.75)	27.0 (6.78)
HBsAg (log_{10} IU/mL), mean (SD)	1.9 (0.62)	2.8 (0.71)	2.6 (0.69)	2.6 (1.15)	3.3 (0.46)	4.1 (0.35)	3.7 (0.38)	3.8 (0.73)	4.3 (0.30)
HBsAg, n (%)									
< 1,000 IU/mL	6 (100)	2 (33.3)	5 (83.3)	3 (50.0)	1 (16.7)	0	0	1 (16.7)	0
1,000 to < 3,000 IU/mL	0	4 (66.7)	1 (16.7)	2 (33.3)	3 (50.0)	0	1 (16.7)	1 (16.7)	0
3,000 to < 10,000 IU/mL	0	0	0	1 (16.7)	1 (16.7)	3 (50.0)	4 (66.7)	2 (33.3)	0
≥ 10,000 IU/mL	0	0	0	0	1 (16.7)	3 (50.0)	1 (16.7)	2 (33.3)	6 (100)

BMI, body mass index; HBsAg, hepatitis B surface antigen; SD, standard deviation; y, years.

VIR-3434 Pharmacokinetics

- PK results are presented relative to baseline HBsAg levels ≤ or > 3,000 IU/mL
- In all cohorts, median time to maximum concentration (T_{max}) was achieved 3 to 6 days after dosing
- The highest free VIR-3434 serum concentration was observed with the 300 mg dose level (**Figure 3**), regardless of baseline HBsAg level

Figure 3. Free VIR-3434 Serum Concentration Profiles Following a Single SC Dose, Stratified by Baseline HBsAg Level



Time (days) = Nominal PK sampling day. Participants with only BLQ values are excluded. BLQ, below limit of quantification (10 ng/mL); HBsAg, hepatitis B surface antigen; SC, subcutaneous; SD, standard deviation.

Table 2. Serum PK Parameters Following a Single SC Dose, Stratified by Baseline HBsAg Level

PK Parameter	HBsAg ≤ 3,000 IU/mL*				HBsAg > 3,000 IU/mL**	
	VIR-3434 6 mg n = 5	VIR-3434 18 mg n = 6	VIR-3434 75 mg n = 8	VIR-3434 300 mg n = 6	VIR-3434 75 mg n = 5	VIR-3434 300 mg n = 11
AUC_{last}, day*ng/mL	**3,130 (67.5)**	**4,760 (225.7)**	**93,000 (66.5)**	**490,000 (77.5)**	**10,300 (692.7)**	**91,400 (366.5)**
C_{max}, ng/mL	**352 (27.0)**	**504 (133.6)**	**5,590 (31.6)**	**21,400 (60.5)**	**4,750 (46.9)**	**15,900 (63.5)**
T_{max}, day	6.90 (1.01, 7.00)	2.95 (1.00, 6.88)	5.44 (0.0417, 8.11)	2.98 (2.11, 6.97)	3.00 (2.95, 3.94)	2.98 (2.86, 6.97)
C_{last}, ng/mL	40.7 (72.8)	23.4 (124.4)	82.4 (220.5)	138 (56.3)	258 (307.2)	1,060 (545.8)
T_{last}, day	15.9 (10.0, 28.9)	41.9 (6.87, 56.0)	39.0 (17.1, 168)	112 (48.9, 112)	11.0 (2.93, 55.9)	14.0 (2.95, 78.9)
CL/F, mL/day	1,950 (NA)[b]	961 (NA)[b]	743 (67.3)[a]	609 (77.4)	1200 (NA)[b]	883 (43.6)[a]
V_z/F, mL	9,420 (NA)[b]	6,280 (NA)[b]	7,010 (24.9)[a]	9,350 (49.7)	8,120 (NA)[b]	6,770 (29.4)[a]
$t_{1/2}$, day	**3.57 (2.33, 4.81)[b]**	**5.08 (3.82, 6.34)[b]**	**6.31 (3.17, 17.2)[a]**	**12.7 (5.96, 16.0)**	**4.25 (2.48, 6.02)[b]**	**7.24 (1.99, 8.45)[a]**

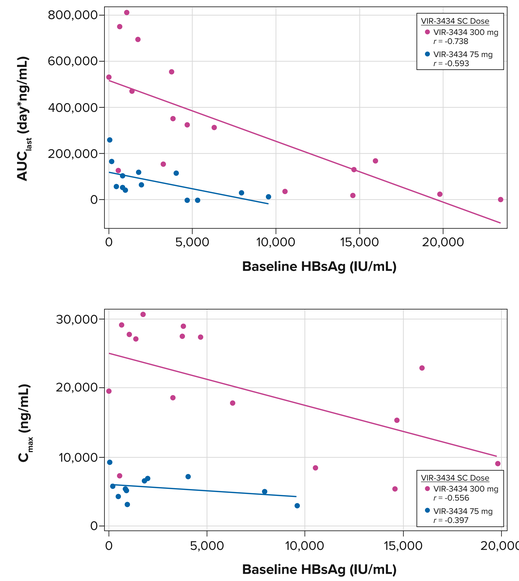
Median (minimum, maximum) are reported for T_{max}, T_{last}, and $t_{1/2}$; geometric mean (geometric CV%) are reported for the other PK parameters. CV% is only reported when n > 2.
PK parameters calculable in [a]n = 7; [b]n = 2, due to $\%AUC_{Extrap}$ > 20%.
*n = 1 with HBsAg ≤ 3,000 IU/ml administered 18 mg group was excluded from PK summary table; parameters not calculable. **n = 1 with HBsAg > 3,000 IU/mL administered 18 mg; therefore, PK parameters were not included in summary table
AUC, area under curve; AUC_{last}, AUC to last measurable concentration; C_{last}, last measurable concentration; CL/F, apparent clearance; C_{max}, maximum concentration; CV%, percent coefficient of variation; HBsAg, hepatitis B surface antigen; NA, not applicable; PK, pharmacokinetic; SC, subcutaneous; T_{last}, time of last measurable concentration; T_{max}, time to reach C_{max}; $t_{1/2}$, half-life; V_z/F, apparent volume of distribution.

- VIR-3434 had a shorter $t_{1/2}$ and faster apparent clearance in participants with higher baseline HBsAg levels (**Table 2**), suggestive of target-mediated drug disposition
  - At the 300 mg dose level, median apparent clearance (CL/F) was 609 mL/day and 883 mL/day in participants with HBsAg ≤ 3,000 IU/mL and > 3,000 IU/mL, respectively. A similar trend was also observed at the 75 mg dose level

Correlation of VIR-3434 PK and baseline HBsAg

- Correlations between PK and HBsAg were assessed for the 75 and 300 mg dose levels
- Correlation plots (**Figure 4**) demonstrate a moderate impact of baseline HBsAg on free VIR-3434 exposure (AUC_{last} and C_{max}) based on Pearson correlation coefficient; the PK exposure is lower in participants with higher baseline HBsAg

Figure 4. PK Exposures (AUC_{last} and C_{max}) Versus Baseline HBsAg Following a Single SC Dose of VIR-3434



r refers to Pearson Correlation Coefficient.
AUC_{last}, area under curve to last measurable concentration; C_{max}, maximum concentration; HBsAg, hepatitis B surface antigen; PK, pharmacokinetics; SC, subcutaneous.

Conclusions

- The highest and most durable free VIR-3434 exposure was observed with the 300 mg dose, irrespective of baseline HBsAg level, consistent with prior data regarding HBsAg reduction[3]
- VIR-3434 had a shorter $t_{1/2}$ and faster apparent clearance in participants with higher baseline HBsAg levels
- Correlation plots demonstrate moderate impact of baseline HBsAg on VIR-3434 AUC_{last} and C_{max}. This is suggestive of target-mediated drug disposition; namely, that free VIR-3434 rapidly binds to HBsAg and is assumed to be cleared from the systemic circulation
- These data support the continued evaluation of VIR-3434 300 mg SC administered every 4 weeks as monotherapy or in combination therapy for chronic HBV and HDV infection

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