PO-839

Rapid HBsAg Reduction in Chronic Hepatitis B Virus Infection: Preliminary Results From a Phase 1 Study Evaluating a Single Dose of VIR-3434, a Novel Neutralizing, Vaccinal Monoclonal Antibody

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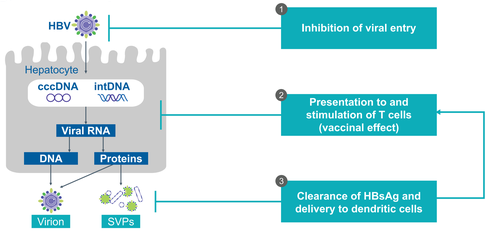
Introduction

- Chronic hepatitis B virus (HBV) infection is a major global public health issue affecting approximately 290 million people worldwide, causing an estimated 900,000 deaths annually[1,2]
- A significant unmet medical need remains for a curative, well-tolerated chronic hepatitis B treatment with a finite duration
- VIR-3434 is currently in clinical development for the treatment of chronic HBV infection. It is an Fc-engineered human monoclonal antibody that targets the conserved antigenic loop of HBsAg
- In Part A of this study, single doses of VIR-3434 of up to 3,000 mg were associated with favorable safety and pharmacokinetics in healthy volunteers[3]

Figure 1. VIR-3434: An Fc-Engineered Human Antibody Against HBsAg, With Multiple Potential Mechanisms of Action

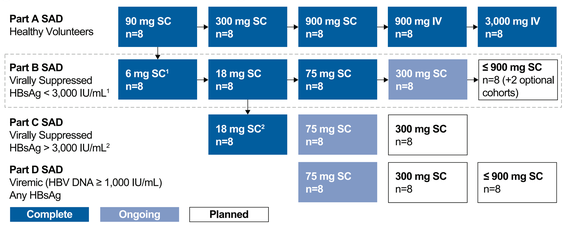


cccDNA, covalently closed circular DNA; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; intDNA, integrated DNA; RNA, ribonucleic acid; SVPs, subviral particles.

Multiple potential modes of action of VIR-3434 (Figure 1)

1. Inhibition of HBV entry into hepatocytes by interfering with the interactions between virions and cell receptors
2. Enhanced immunologic activity via an engineered Fc region containing the *XX2/GAALIE* mutation that increases engagement of activating FcγIIa and IIIa receptors, and diminishes binding to inhibitory FcγIIb receptors on dendritic cells, resulting in the generation of T cells (vaccinal effect)
3. Clearance of HBsAg and delivery to dendritic cells

Figure 2. VIR-3434-1002 Design



[1]The 6 mg SC cohort in Part B enrolled participants with screening HBsAg < 1,000 IU/mL.
[2]The 18 mg SC cohort in Part C enrolled participants with any screening HBsAg.
IV, intravenous; SAD, single ascending dose; SC, subcutaneous.

- In Part B, 8 participants per cohort were randomized in a 6:2 ratio to receive a single dose of VIR-3434 or placebo by SC injection
- Preliminary blinded safety and tolerability results and HBsAg data up to at least 4 weeks post-dose are presented for Part B cohorts evaluating doses of 6 mg, 18 mg, and 75 mg

Part B Objectives

Primary

- To evaluate the safety and tolerability of VIR-3434 in adult participants with chronic HBV infection without cirrhosis

Secondary

- To assess the antiviral activity of VIR-3434 in adult participants with chronic HBV infection without cirrhosis
- To characterize the serum PK of VIR-3434 in adult participants with chronic HBV infection without cirrhosis
- To evaluate the immunogenicity (induction of ADA) of VIR-3434 in adult participants with chronic HBV infection without cirrhosis

ADA, antidrug antibodies; PK, pharmacokinetics.

Key Entry Criteria for Part B

Inclusion

- Age 18 to 65 years
- Chronic HBV infection
- HBV DNA < 100 IU/mL
- Negative anti-HBs
- On NRTI therapy for ≥ 2 months
- HBeAg-negative
- HBsAg < 3,000 IU/mL[1]

Exclusion

- Significant fibrosis or cirrhosis
- ALT or AST > 2 x ULN
- Active infection with HIV, HCV, or hepatitis Delta virus
- CrCl < 75 mL/min (Cockcroft-Gault)

[1]The 6 mg SC cohort in Part B enrolled participants with HBsAg < 1,000 IU/mL.
ALT, alanine aminotransferase; anti-HBs, hepatitis B surface antibody; AST, aspartate aminotransferase; CrCl, creatinine clearance; HBeAg, hepatitis B e antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NRTI, nucleos(t)ide reverse transcriptase inhibitor; ULN, upper limit of normal.

Table 1. Demographics and Baseline Characteristics

	VIR-3434 or Placebo		
	6 mg SC N=8	18 mg SC N=8	75 mg SC N=8
Age (y), mean (range)	56.5 (48-64)	48.8 (40-60)	50.1 (39-62)
Sex, n (%)			
Men	8 (100.0)	7 (87.5)	6 (75.0)
Women	0	1 (12.5)	2 (25.0)
Race, n (%)			
Asian	4 (50.0)	4 (50.0)	5 (62.5)
Black or African American	1 (12.5)	1 (12.5)	0
White	3 (37.5)	3 (37.5)	2 (25.0)
Other	0	0	1 (12.5)
BMI (kg/m^2), median (range)	26 (23.1-30.0)	26 (20.2-31.4)	24 (22.3-31.7)
Baseline HBsAg[1] (IU/mL), mean (range)	197 (7.6-545.9)	837 (22.2-1560.2)	814 (22.0-2289.2)
< 1,000 IU/mL, n (%)	8 (100.0)	4 (50.0)	6 (75.0)
< 100 IU/mL, n (%)	4 (50.0)	2 (25.0)	2 (25.0)

[1]Mean baseline HBsAg in the 6 mg SC cohort was lower due to inclusion criteria: The 6 mg SC cohort enrolled participants with screening HBsAg < 1,000 IU/mL; The 18 mg SC and 75 mg cohorts enrolled participants with screening HBsAg < 3,000 IU/mL.
BMI, body mass index; SC, subcutaneous.

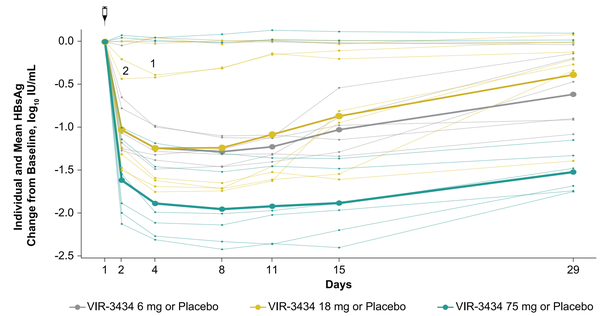
Table 2. Preliminary Summary of Safety and Tolerability Data

	VIR-3434 or Placebo			
n (%)	6 mg SC N=8	18 mg SC N=8	75 mg SC N=8	Total N=24
Any AE	2 (25.0)	4 (50.0)	4 (50.0)	19 (33)
Grade 1	2 (25.0)	3 (37.5)	3 (37.5)	8 (33.3)
Grade 2	0	1 (12.5)	1 (12.5)	2 (8.3)
Grade ≥ 3	0	0	0	0
Treatment-related	1 (12.5)	0	2 (25.0)	3 (12.5)
SAE	0	0	0	0
Study discontinuations	0	0	0	0

AE, adverse event; SAE, serious adverse event; SC, subcutaneous.

- Across all cohorts, 3 participants reported a total of 4 Grade 1 AEs that were deemed related to VIR-3434: palpitations, headache, musculoskeletal stiffness, and nasopharyngitis
- One participant in the 6 mg cohort experienced a Grade 1 ALT elevation at 24 weeks post-dose
- No clinically significant laboratory abnormalities or changes in liver safety parameters were observed
- No participant developed clinical or laboratory signs of immune complex disease

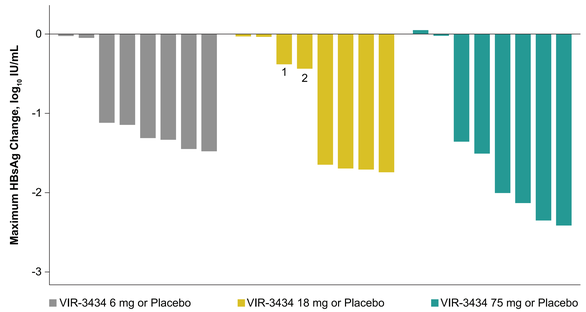
Figure 3. Preliminary HBsAg Kinetics Over Time



Mean curves (shown in bold) exclude 2 participants per cohort with < 0.2 log10 IU/mL change from baseline.
[1]Free VIR-3434 was undetectable in all available samples.
[2]Free VIR-3434 concentrations were lower than anticipated in all available samples.
HBsAg measured with Abbott ARCHITECT®.

- Most participants rapidly achieved a > 1 $\log_{10}$ IU/mL decline in HBsAg within approximately 1 week post-dose
- Most participants achieved HBsAg < 100 IU/mL at nadir
  - Excluding those presumed to have received placebo, 5 of 6 participants in the 75 mg cohort (all of whom had a baseline HBsAg > 10 IU/mL) achieved HBsAg < 10 IU/mL at nadir
- Mean HBsAg reductions were similar in the 6 mg and 18 mg cohorts
  - Two participants in the 18 mg cohort had undetectable or lower-than-expected free PK and < 0.5 $\log_{10}$ IU/mL reductions in HBsAg

Figure 4. Maximum HBsAg Change From Baseline



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HBsAg measured with Abbott ARCHITECT®.

- The largest (> 2 $\log_{10}$ IU/mL) and most sustained reductions in HBsAg were observed in the 75 mg cohort (**Figures 3 and 4**)
  - Mean reduction was 1.96 $\log_{10}$ IU/mL at nadir and 1.5 $\log_{10}$ IU/mL at Day 29

Conclusions

- In virally suppressed participants with HBsAg < 3,000 IU/mL, a single dose of 6 mg to 75 mg of VIR-3434 resulted in rapid HBsAg reductions of > 1 $\log_{10}$ IU/mL in most participants
- Single doses of VIR-3434 were generally well tolerated; all AEs were Grade 1 or 2
- These data support the potential for VIR-3434 to have a meaningful role in the functional cure of chronic HBV infection
- Ongoing studies are evaluating VIR-3434
  - At higher single doses
  - In participants with higher baseline HBsAg values and in those with viremia
  - In combination with VIR-2218—an siRNA targeting the HBx region of the HBV genome—in the Phase 2 MARCH study

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References: 1. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol*. 2018;3(6):383-403. **2.** Hepatitis B. World Health Organization. July 27, 2020. Accessed April 8, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. **3.** Gupta SV, et al. Preliminary pharmacokinetics and safety in healthy volunteers of VIR-3434, a monoclonal antibody for the treatment of chronic hepatitis B infection. PO-43. Presented at The International Liver Congress, 2021.

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