Safety and Efficacy of VIR-2218 With or Without Pegylated Interferon Alfa in Virally-Suppressed Participants With Chronic Hepatitis B Virus Infection: Post-treatment Follow Up

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Current research interests include:

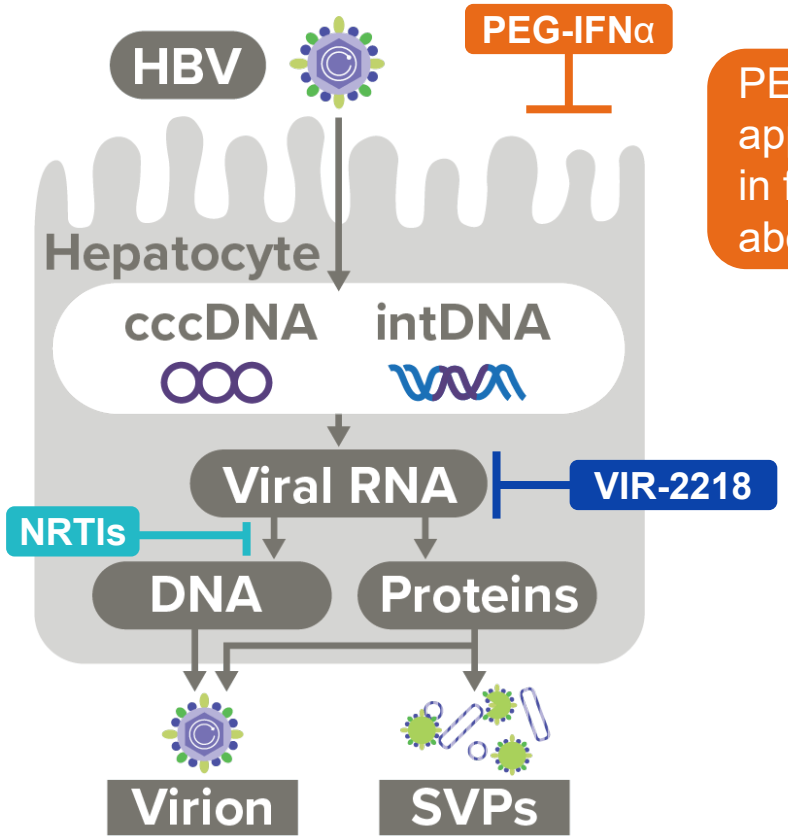
- Novel antiviral and immunomodulatory agents for HBV
- Treatment effects on HBV DNA host integration
- Development of emerging biomarkers for overt and occult hepatitis B infection
- Disease interaction between HBV and NAFLD

Abbreviations: DNA, deoxyribonucleic acid; HBV, hepatitis B virus; NAFLD, nonalcoholic fatty liver disease.

Introduction

- Preliminary data have shown that combining VIR-2218 and PEG-IFNα results in deeper HBsAg declines compared with VIR-2218 alone[1]

- We hypothesize that lowering HBsAg with VIR-2218 in the context of immune stimulation by PEG-IFNα may lead to HBsAg seroclearance in a greater proportion of patients

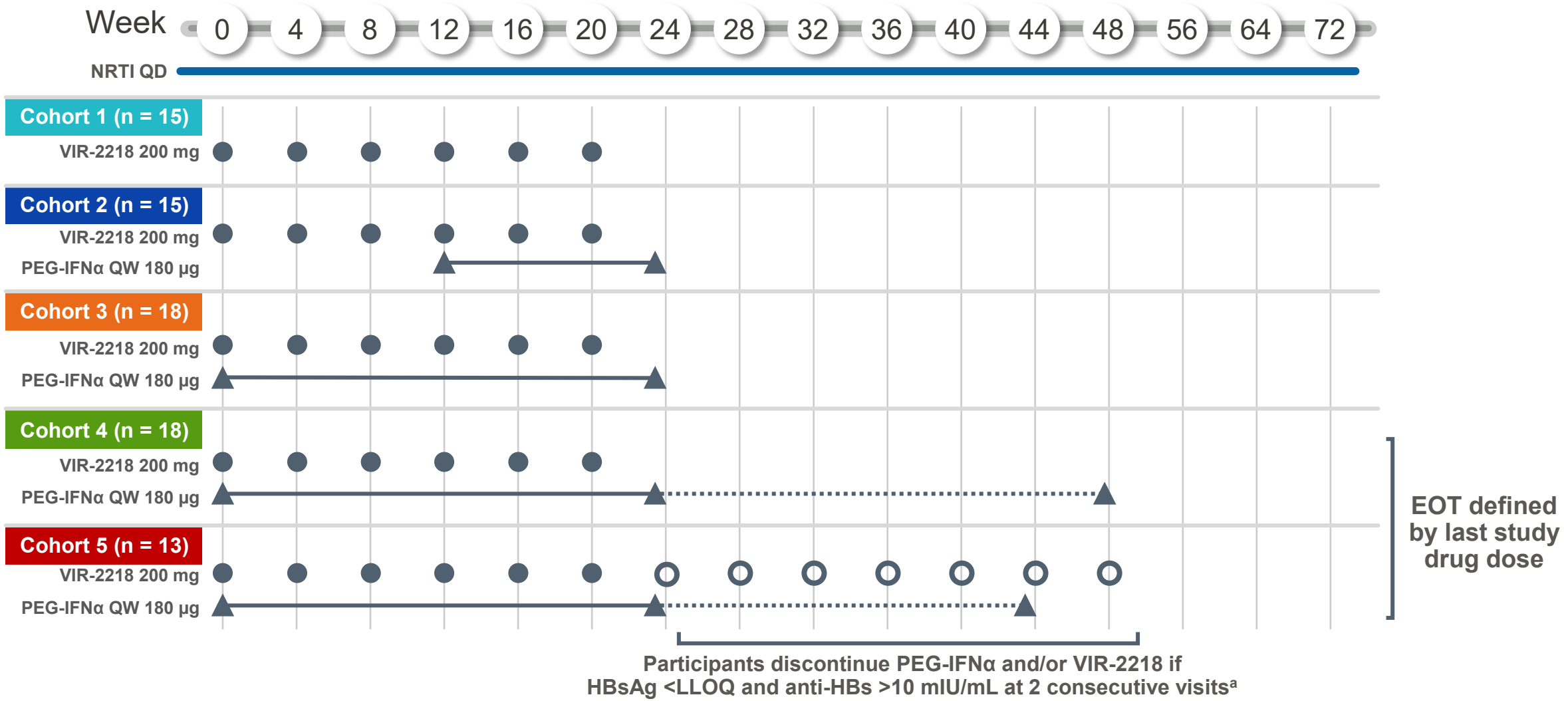


PEG-IFNα is the only approved therapy to result in functional cure, but in only about 3% to 7% of patients[2]

VIR-2218 is a GalNAc-conjugated ESC+ siRNA targeting the HBx region of HBV genome that reduces HBsAg in patients with chronic HBV infection[3]

1. Yuen MF, et al. Hepatology 2022; 76:S18; **2.** EASL. *J Hepatol.* 2017;67:370-398; **3.** Gane E, et al. J Hepatol 2021;75(2): S287.
Abbreviations: EASL, European Association for the Study of the Liver; cccDNA, covalently closed circular DNA; intDNA, integrated DNA; ESC+, enhanced stabilization chemistry plus; GalNAc, trivalent N-acetylgalactosamine; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBx, hepatitis B virus X protein; PEG-IFNα, pegylated interferon alfa-2a; RNA, ribonucleic acid; siRNA, small interfering RNA; SVPs, subviral particles.

A Phase 2 Trial Evaluating VIR-2218 With and Without PEG-IFNα



[a]HBsAg assay LLOQ and LLOD are 0.05 IU/mL.

Abbreviations: EOT, end of treatment; HBsAg, hepatitis B surface antigen; LLOD, lower limit of detection; LLOQ, lower limit of quantitation; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PEG-IFNα, pegylated interferon alfa-2a; QD, daily; QW, every week; anti-HBs, hepatitis B surface antibody.

Key Inclusion/Exclusion Criteria

Inclusion

- Age 18 to 65 years (inclusive)
- Chronic HBV infection defined as positive serum HBsAg for ≥6 months
- On NRTI therapy for ≥2 months
- HBsAg >50 IU/mL
- HBV DNA <90 IU/mL

Exclusion

- Significant fibrosis or cirrhosis (FibroScan >8.5 kPa at screening or Metavir F3/F4 liver biopsy within 1 year)
- Bilirubin, INR, or prothrombin time >ULN
- ALT or AST >2 x ULN
- Active HIV, HCV, or HDV infection

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D Virus; HIV, human immunodeficiency virus; INR, international normalised ratio; NRTI, nucleos(t)ide reverse transcriptase inhibitor; ULN, upper limit of normal.

Demographics and Baseline Characteristics

Participants	Cohort 1 (n = 15)	Cohort 2 (n = 15)	Cohort 3 (n = 18)	Cohort 4 (n = 18)	Cohort 5 (n = 13)
	VIR-2218 x 6	VIR-2218 x 6 lead-in + PEG-IFNα x 12	VIR-2218 x 6 + PEG-IFNα x 24	VIR-2218 x 6 + PEG-IFNα x ≤48	VIR-2218 x 13 + PEG-IFNα x ≤44
HBeAg-positive, n (%)	4 (26.7)	6 (40.0)	7 (38.9)	6 (33.3)	3 (23.1)
Age (years), mean (SD)	50.3 (8.6)	46.6 (7.8)	48.7 (5.8)	45.2 (9.4)	48.5 (7.6)
Male (sex), n (%)	13 (86.7)	13 (86.7)	14 (77.8)	15 (83.3)	7 (53.8)
Race, n (%)					
Asian	12 (80.0)	13 (86.7)	16 (88.9)	18 (100.0)	13 (100.0)
White	0	0	1 (5.6)	0	0
Other	3 (20.0)	2 (13.3)	1 (5.6)	0	0
HBsAg (log_{10} IU/mL), median (range)	3.4 (2.6, 4.1)	3.2 (2.2, 4.0)	3.4 (2.2, 4.2)	2.9 (1.9, 4.3)	3.7 (2.1, 4.4)
ALT (U/L), mean (SD)	21.5 (10.1)	25.0 (12.4)	21.7 (12.0)	19.7 (7.1)	22.6 (10.1)
ALT >ULN, n (%)	1 (6.7)	1 (6.7)	1 (5.6)	0	1 (7.7)

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; PEG-IFNα, pegylated interferon alfa-2a; SD, standard deviation; ULN, upper limit of normal.

VIR-2218 With or Without PEG-IFNα Was Generally Well Tolerated

Participants, n (%)	Cohort 1 (n = 15)	Cohort 2 (n = 15)	Cohort 3 (n = 18)	Cohort 4 (n = 18)	Cohort 5 (n = 13)
	VIR-2218 x 6	VIR-2218 x 6 lead-in + PEG-IFNα x 12	VIR-2218 x 6 + PEG-IFNα x 24	VIR-2218 x 6 + PEG-IFNα x ≤48	VIR-2218 x 13 + PEG-IFNα x ≤44
Any TEAEs[a]	9 (60.0)	13 (86.7)	16 (88.9)	17 (94.4)	13 (100.0)
Grade 1	7 (46.7)	9 (60.0)	7 (38.9)	10 (55.6)	4 (30.8)
Grade 2	2 (13.3)	4 (26.7)	7 (38.9)	4 (22.2)	6 (46.2)
Grade 3	0	0	2 (11.1)	2 (11.1)	3 (23.1)
Grade 4	0	0	0	1 (5.6)	0
Treatment-related TEAEs[a]	3 (20.0)	12 (80.0)	13 (72.2)	15 (83.3)	13 (100.0)
Related to VIR-2218	3 (20.0)	4 (26.7)	8 (44.4)	7 (38.9)	6 (46.2)
Related to PEG-IFNα	N/A	12 (80.0)	12 (66.7)	14 (77.8)	13 (100.0)
Related to VIR-2218 and PEG-IFNα	N/A	1 (6.7)	5 (27.8)	3 (16.7)	4 (30.8)
SAE[b]	0	0	1 (5.6)	1 (5.6)	1 (7.7)
Study discontinuation due to TEAE	0	0	0	0	0

- Most TEAEs were consistent with the known effects of PEG-IFNα
- No SAEs were related to VIR-2218

[a]TEAE is defined as any AE with onset after study drug start and within 30 days of the last dose of study drug.
[b]3 SAEs have been reported: ankle fracture (Cohort 3, n = 1), gall bladder pain (Cohort 5, n = 1) unrelated to study treatments, and mania (Cohort 4, n = 1) related to PEG-IFNα.
Abbreviations: AE, adverse event; N/A, not applicable; PEG-IFNα, pegylated interferon alfa-2a; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

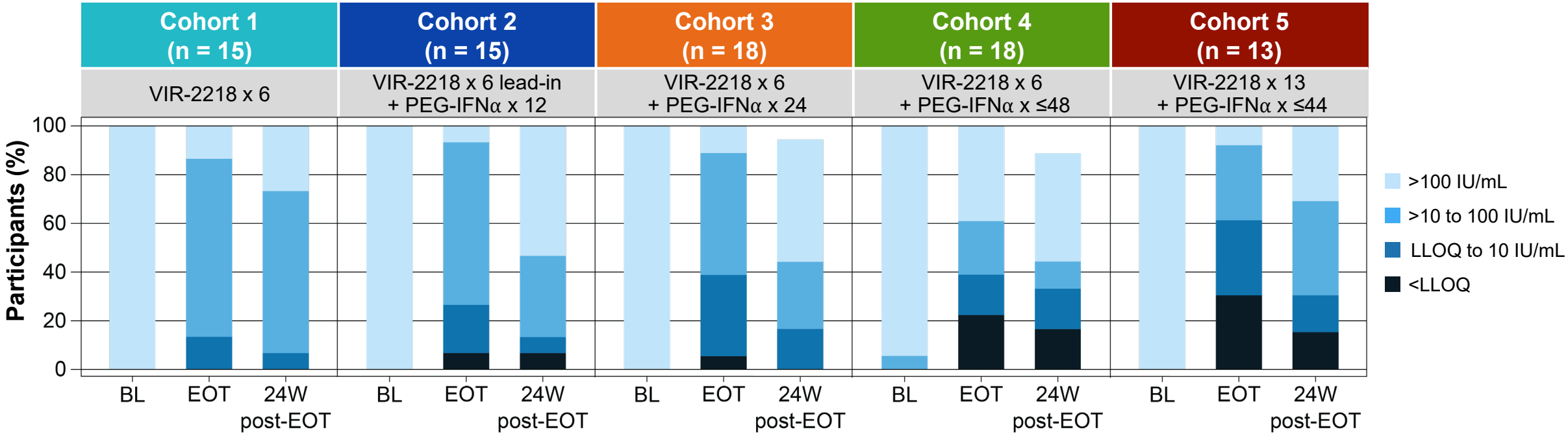
Effects on ALT, Neutrophil, and Platelet Levels Were Consistent With Known Effects of PEG-IFNα

Participants, n (%)	Cohort 1 (n = 15)	Cohort 2 (n = 15)	Cohort 3 (n = 18)	Cohort 4 (n = 18)	Cohort 5 (n = 13)
	VIR-2218 x 6	VIR-2218 x 6 lead-in + PEG-IFNα x 12	VIR-2218 x 6 + PEG-IFNα x 24	VIR-2218 x 6 + PEG-IFNα x ≤48	VIR-2218 x 13 + PEG-IFNα x ≤44
ALT level increase					
Grade 1	2 (13.3)	12 (80.0)	12 (66.7)	14 (77.8)	9 (69.2)
Grade 2	0	1 (6.7)	2 (11.1)	2 (11.1)	2 (15.4)
Grade 3	0	0	1 (5.6)	1 (5.6)	0
Neutrophil level decrease					
Grade 1	3 (20.0)	4 (26.7)	4 (22.2)	1 (5.6)	1 (7.7)
Grade 2	1 (6.7)	8 (53.3)	10 (55.6)	6 (33.3)	6 (46.2)
Grade 3	0	2 (13.3)	3 (16.7)	10 (55.6)	6 (46.2)
Grade 4	0	0	0	1 (5.6)	0
Platelet level decrease					
Grade 1	1 (6.7)	10 (66.7)	10 (55.6)	14 (77.8)	9 (69.2)

- Majority of ALT elevations resolved within 24 weeks post-EOT
- Majority of neutrophil and platelet abnormalities resolved within 4 weeks post-EOT[a]

[a]Neutrophils and platelets were assessed through Week 48
Grading defined by CTCAE
Abbreviations: ALT, alanine transaminase; CTCAE, Common Terminology Criteria for Adverse Events; PEG-IFNα, pegylated interferon alfa-2a.

Longer Duration of Combination Treatment Resulted in Greater HBsAg Decline and Rates of Seroclearance



- HBsAg seroclearance[a] was observed only in participants receiving the combination of VIR-2218 and PEG-IFNα
- Compared with other cohorts, more participants (62% [8/13]) in Cohort 5 achieved HBsAg levels <10 IU/mL at EOT
  - 69% (9/13) of participants sustained HBsAg levels <100 IU/mL at 24-weeks post-EOT

[a]Seroclearance defined as HBsAg <0.05 IU/mL (LLOQ).
Abbreviations: BL, baseline; EOT, end of treatment; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantitation; PEG-IFNα, pegylated interferon alfa-2a; W, weeks.

Longer Treatment Durations Were Associated With Higher Rates of HBsAg Seroclearance

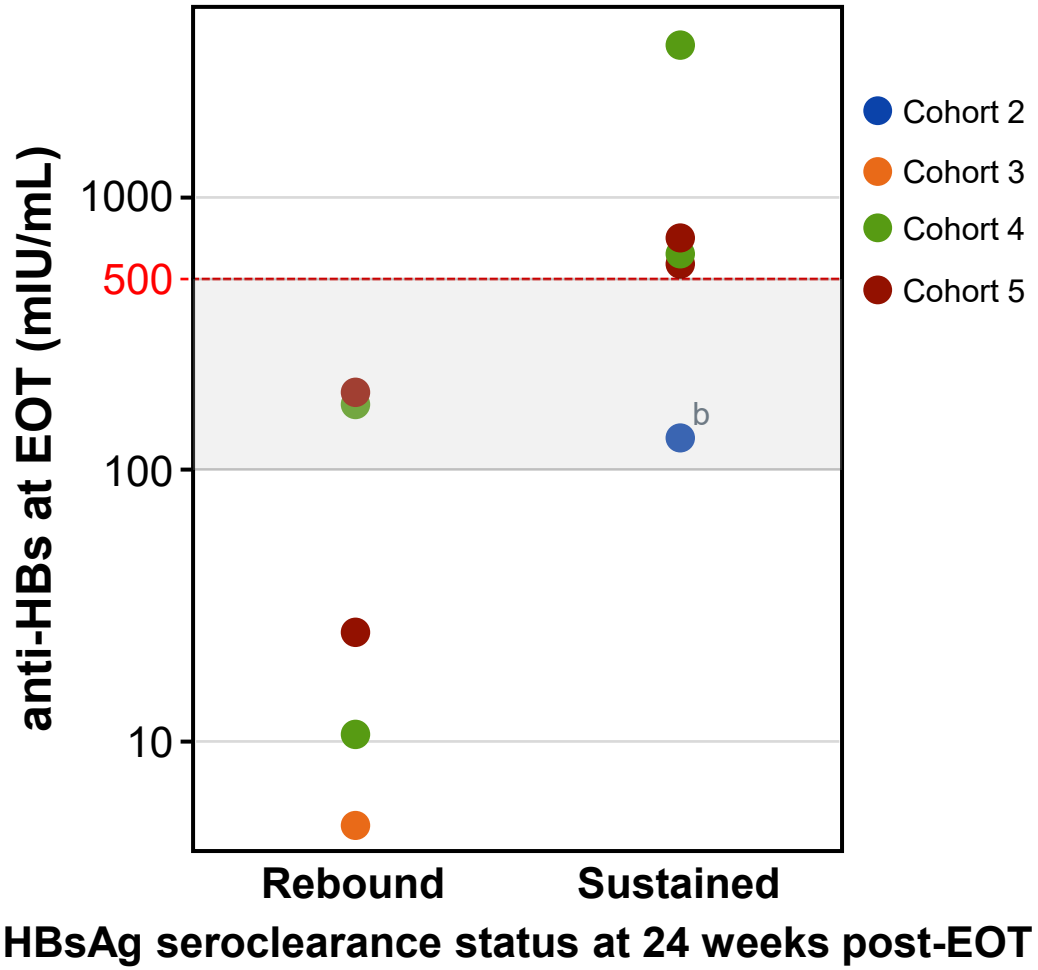
Participants with HBsAg seroclearance, n (%)	Cohort 1 (n = 15)	Cohort 2 (n = 15)	Cohort 3 (n = 18)	Cohort 4 (n = 18)	Cohort 5 (n = 13)
	VIR-2218 x 6	VIR-2218 x 6 lead-in + PEG-IFNα x 12	VIR-2218 x 6 + PEG-IFNα x 24	VIR-2218 x 6 + PEG-IFNα x ≤48	VIR-2218 x 13 + PEG-IFNα x ≤44
At EOT[a]	0 (0)	1 (6.7)	1 (5.6)	4 (22.2)	4 (30.8)
At 24 weeks post-EOT	0 (0)	1 (6.7)	0 (0)	3[b] (16.7)	2 (15.4)
HBsAg at baseline					
<1,000 IU/mL	0/3 (0)	1/5 (20)	0/6 (0)	2/10 (20)	1/5 (20)
>1000 IU/mL	0/12 (0)	0/10 (0)	0/12 (0)	1/8 (12.5)	1/8 (12.5)
HBeAg at baseline					
HBeAg-positive	0/4 (0)	0/6 (0)	0/7 (0)	1/6 (16.7)	1/3 (33.3)
HBeAg-negative	0/11 (0)	1/9 (11.1)	0/11 (0)	2/12 (16.7)	1/10 (10)

- Among 31 participants receiving 48-week regimens of VIR-2218 and PEG-IFNα
  - 8 (25.8%) had HBsAg seroclearance at EOT
  - 5 (16.1%) sustained HBsAg seroclearance at 24 weeks post-EOT
- All participants who had HBsAg rebounds after seroclearance maintained levels <100 IU/mL at 24 weeks post-EOT

[a]End of treatment refers to the last day of study drug administration; in cohorts 4 and 5 some participants met efficacy criteria to stop treatment early.
[b]Two participants with HBsAg seroclearance at EOT had rebounds; an additional participant had HBsAg seroclearance after EOT but maintained it through 24 weeks post-EOT.
Seroclearance defined as HBsAg <0.05 IU/mL (LLOQ).
Abbreviations: EOT, end of treatment; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantitation; PEG-IFNα, pegylated interferon alfa-2a.

Higher Anti-HBs Titer at EOT Predicts HBsAg Seroclearance Durability

- Among participants who had HBsAg seroclearance by EOT[a]:
  - All participants (4/4) with anti-HBs levels >500 mIU/mL at EOT had sustained HBsAg seroclearance at 24 weeks post-EOT
  - All participants (3/3) with anti-HBs <100 mIU/mL at EOT experienced a rebound in HBsAg
  - Three participants had anti-HBs levels between 100–500 mIU/mL; 2 experienced a rebound, and 1 sustained HBsAg seroclearance through 24 weeks post-EOT



[a] One participant had HBsAg seroclearance after EOT and is not included in the analyses.
[b] Participant had anti-HBs >1,500 mIU/mL 4 weeks after EOT.
Seroclearance defined as HBsAg <0.05 IU/mL (LLOQ).
Abbreviations: EOT, end of treatment; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantitation.

Summary of Results

- VIR-2218 alone and in combination with PEG-IFNα was generally well tolerated
  - Most adverse events were as expected with PEG-IFNα and resolved after EOT
  - No participants discontinued the study due to TEAEs
- Among participants receiving 48 weeks of concurrent VIR-2218 plus PEG-IFNα:
  - 31% (4/13) had HBsAg seroclearance at EOT
  - 15% (2/13) had sustained HBsAg seroclearance for 24 weeks post-EOT
- Longer durations of treatment with both VIR-2218 and PEG-IFNα were associated with greater HBsAg decline and a higher incidence of HBsAg seroclearance
- Anti-HBs titers >500 mIU/mL at EOT were associated with sustained HBsAg seroclearance at 24 weeks post-EOT
- Additional follow up is ongoing

Seroclearance defined as HBsAg <0.05 IU/mL (LLOQ).
Abbreviations: EOT, end of treatment; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantitation; PEG-IFNα, pegylated interferon alfa-2a; TEAE, treatment-emergent adverse event.

Key Takeaways

- Antiviral activity of VIR-2218 can be potentiated by immunomodulatory effects of PEG-IFNα to achieve sustained HBsAg seroclearance for at least 24 weeks after the end of treatment
- This proof-of-concept phase 2 study supports the evaluation of VIR-2218 and PEG-IFNα with VIR-3434 in Part B of the ongoing MARCH study[1]

1. Gane et al, 2023; EASL. Abstract# OS-031.
Abbreviations: HBsAg, hepatitis B surface antigen; PEG-IFNα, pegylated interferon alfa-2a.

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