Preliminary Results From a Phase 2 Study Evaluating VIR-2218 Alone and in Combination With Pegylated Interferon Alfa-2a in Participants With Chronic Hepatitis B Infection

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His 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

Disclosures

- Dr. Man-Fung Yuen serves as advisor/consultant for AbbVie, Arbutus Biopharma, Bristol-Myers Squibb, ClearB Therapeutics, Dicerna Pharmaceuticals, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp & Dohme, Spring Bank Pharmaceuticals, Roche, and Vir Biotechnology
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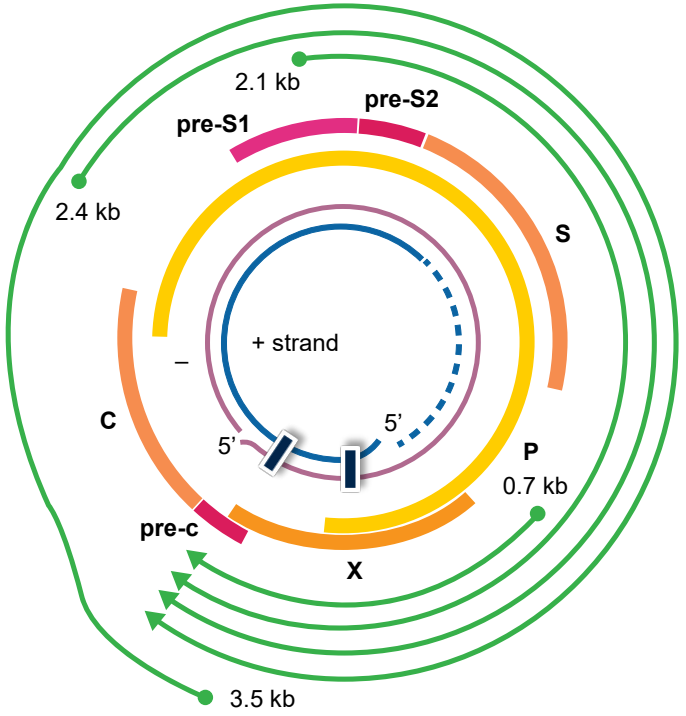
VIR-2218 Targets the HBx Region of the HBV Genome to Silence HBV Transcripts

- VIR-2218 is a GalNAc-conjugated ESC+ siRNA, targeting a conserved site in the HBx coding region, that has been shown to reduce HBsAg in patients with chronic HBV infection[1]
- PEG-IFNα is an immunomodulatory agent with antiviral properties that is approved for use in chronic HBV infection
  - Incidence of HBsAg loss following PEG-IFNα monotherapy is generally ≤ 7%[2]
- We hypothesize that lowering HBsAg with VIR-2218 in the context of immune stimulation by PEG-IFNα may lead to functional cure in a greater proportion of patients

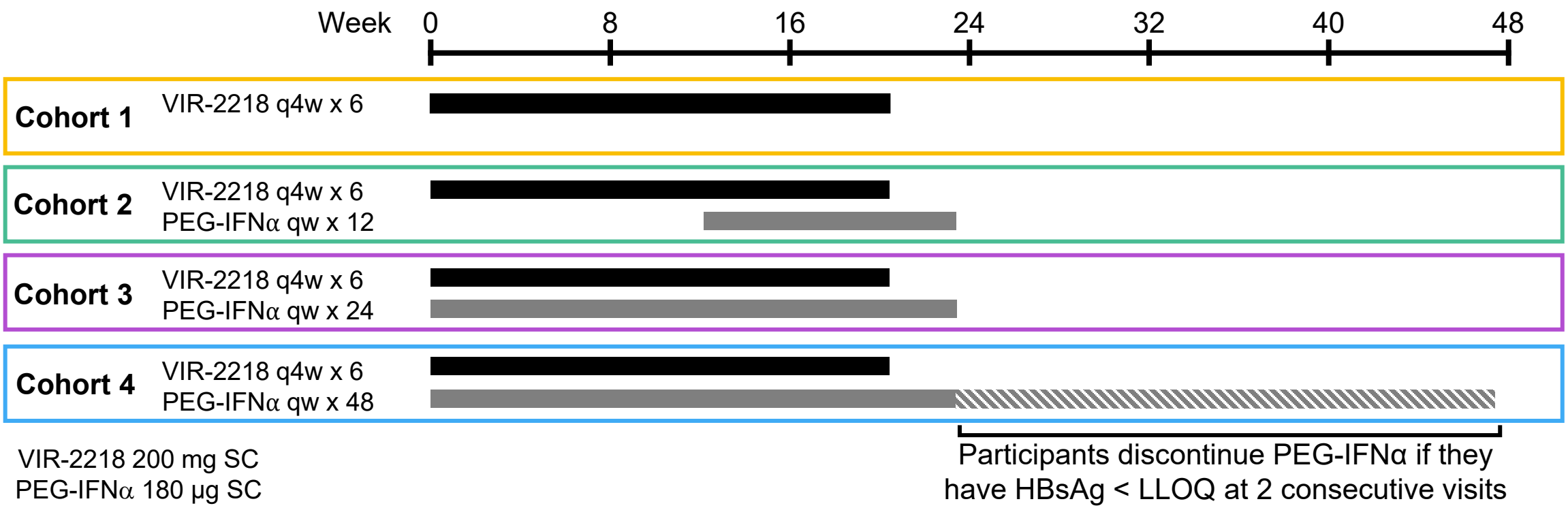


siRNA targeting an overlapping region can silence all transcripts

EASL, European Association for the Study of the Liver; ESC+, enhanced stabilization chemistry plus; GalNAc, trivalent N-acetylgalactosamine; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PEG-IFNα, peginterferon alfa-2a; RNA, ribonucleic acid; siRNA, small interfering RNA.

1. Gane E, et al; 2021 EASL; 2. EASL. J Hepatol. 2017;67:370-398.

A Phase 2 Trial Evaluating VIR-2218 With and Without Peginterferon Alfa-2a



- All participants are virally suppressed
- Preliminary data from Cohorts 1-4 through Week 24 are presented herein

HBsAg assay LLOQ and LLOD are 0.05 IU/mL.
LLOD, lower limit of detection; LLOQ, lower limit of quantitation; q4w, every 4 weeks; qw, every week; µg, microgram; PEG-IFNα, peginterferon alfa-2a, SC, subcutaneous.

Key Inclusion/Exclusion Criteria

Inclusion

- Age 18 to 65 years
- Detectable 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

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DNA, deoxyribonucleic acid; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HDV, hepatitis D virus; INR, international normalized ratio; kPa, kilopascals; NRTI, nucleos(t)ide reverse transcriptase inhibitor; ULN, upper limit of normal.

Demographics and Baseline Characteristics

	Cohort 1 (N=15)	Cohort 2 (N=15)	Cohort 3 (N=18)	Cohort 4 (N=16)
	VIR-2218 only	VIR-2218 lead in + PEG-IFNα (12 wk)	VIR-2218 + PEG-IFNα (24 wk)	VIR-2218 + PEG-IFNα (≤ 48 wk)
HBeAg-positive, n (%)	4 (26.7)	6 (40.0)	7 (38.9)	4 (25.0)
Age (years), mean (SD)	50.3 (8.6)	46.6 (7.8)	48.7 (5.8)	46.0 (9.4)
Male (sex), n (%)	13 (86.7)	13 (86.7)	14 (77.8)	13 (81.3)
Race, n (%)				
Asian	11 (73.3)	13 (86.7)	16 (88.9)	16 (100.0)
White	0	0	1 (5.6)	0
Other	4 (26.7)	2 (13.3)	1 (5.6)	0
HBsAg (log_{10} IU/mL), mean (SD)	3.44 (0.447)	3.20 (0.676)	3.28 (0.726)	2.80 (0.811)
ALT (U/L), mean (SD)	21.5 (10.1)	25.0 (12.4)	21.7 (12.0)	19.2 (7.0)
ALT > ULN, n (%)	1 (6.7)	1 (6.7)	1 (5.6)	0

HBeAg, hepatitis B e antigen; PEG-IFNα, peginterferon alfa-2a; ALT, alanine aminotransferase; SD, standard deviation; wk, week.

Preliminary Safety and Tolerability Up to Week 24

Participants, n (%)	Cohort 1 (N=15)	Cohort 2 (N=15)	Cohort 3 (N=18)	Cohort 4 (N=16)
	VIR-2218 only	VIR-2218 lead in + PEG-IFNα (12 wk)	VIR-2218 + PEG-IFNα (24 wk)	VIR-2218 + PEG-IFNα (≤ 48 wk)
Any TEAEs	9 (60.0)	13 (86.7)	16 (88.9)	11 (68.8)
Grade 1	7 (46.7)	10 (66.7)	6 (33.3)	5 (31.3)
Grade 2	2 (13.3)	3 (20.0)	8 (44.4)	5 (31.3)
Grade 3	0	0	2 (11.1)	1 (6.3)
Treatment-related TEAEs	3 (20.0)	12 (80.0)	14 (77.8)	11 (68.8)
TEAEs related to VIR-2218	3 (20.0)	4 (26.7)	9 (50.0)	7 (43.8)
TEAEs related to PEG-IFNα	N/A	12 (80.0)	13 (72.2)	10 (62.5)
SAE	0	0	1 (5.6)	0
Treatment discontinuation due to AE	0	0	1 (5.6)	0

- The majority of TEAEs were Grade 1 or 2
  - Two PEG-IFNα-related Grade 3 laboratory abnormalities resulted in drug interruption in 1 participant and dose reduction in the other
- One SAE (Grade 3 ankle fracture in Cohort 3) was reported as not related to treatment
- Higher incidence of TEAEs was reported in PEG-IFNα-containing cohorts
  - The most common PEG-IFNα-related events were ISR and pyrexia, each of which occurred in 9 participants
- One participant (Cohort 3) discontinued at Week 4 due to PEG-IFNα-related Grade 2 depression, which was subsequently resolved

TEAE is defined as any AE with onset after study drug start and within 30 days of the last dose.

AE, adverse event; ISR, injection-site reaction; N/A, not applicable; PEG-IFNα, peginterferon alfa-2a; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Trends in ALT, Neutrophils, and Platelets Have Been Consistent With Known Effects of PEG-IFNα

Participants, n (%)	Cohort 1 (N=15)	Cohort 2 (N=15)	Cohort 3 (N=18)	Cohort 4 (N=16)
	VIR-2218 only	VIR-2218 lead-in + PEG-IFNα (12 wk)	VIR-2218 + PEG-IFNα (24 wk)	VIR-2218 + PEG-IFNα (≤ 48 wk)
ALT elevation				
Grade 1	2 (13.3)	12 (80.0)	12 (66.7)	11 (68.8)
Grade 2	0	1 (6.7)	2 (11.1)	0
Grade 3	0	0	1* (5.6)	1* (6.3)
Neutrophil count decreased				
Grade 1	3 (20.0)	4 (26.7)	4 (22.2)	1 (6.3)
Grade 2	1 (6.7)	8 (53.3)	10 (55.6)	7 (43.8)
Grade 3	0	2 (13.3)	3 (16.7)	5 (31.3)
Platelet count decreased				
Grade 1	1 (6.7)	10 (66.7)	10 (55.6)	10 (62.5)

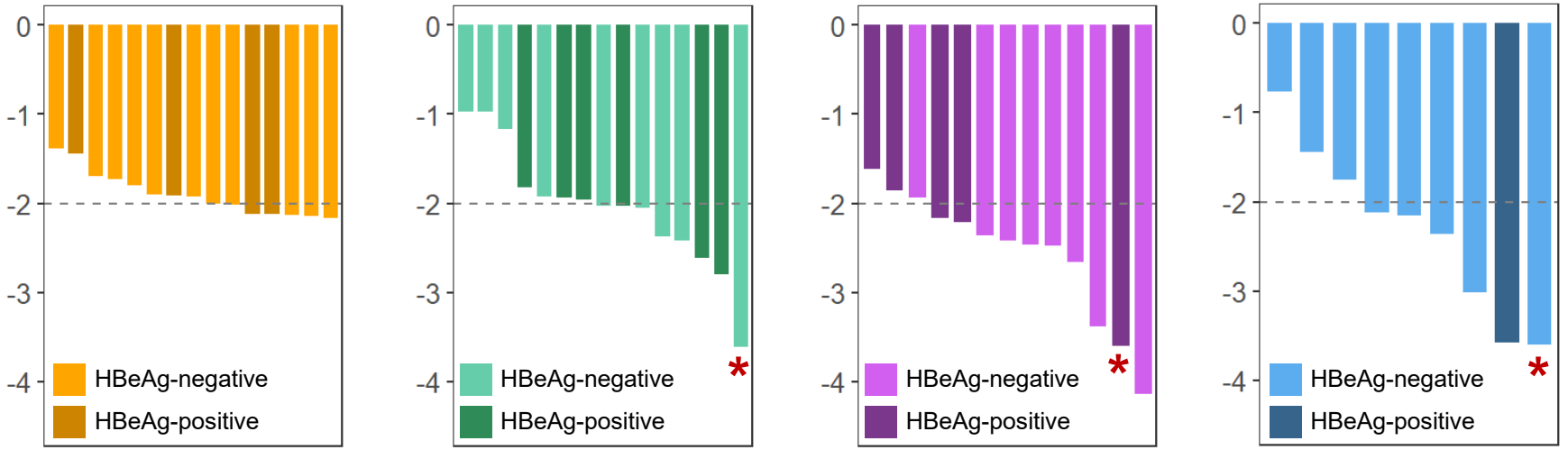
*Two participants had Grade 3 ALT elevations. Maximum ALT was 267 U/L in the Cohort 3 participant and 243 U/L in the Cohort 4 participant.
Grade based on CTCAE v5.0.

CTCAE, Common Terminology Criteria for Adverse Events; ALT, alanine aminotransferase; PEG-IFNα, peginterferon alfa-2a.

Concurrent Initiation of VIR-2218 and PEG-IFNα Combination Achieved Greatest Reductions in HBsAg Through Week 24

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
	VIR-2218 only	**VIR-2218 lead-in + PEG-IFNα (12 wk)**	**VIR-2218 + PEG-IFNα (24 wk)**	**VIR-2218 + PEG-IFNα (≤ 48 wk)**
Week 4, n	15	15	17	13
Mean Change in HBsAg (log_{10} IU/mL)	-0.51	-0.51	-0.92	-1.01
Week 12, n	14	15	16	11
Mean Change in HBsAg (log_{10} IU/mL)	-1.39	-1.42	-1.98	-2.05
At Week 24, n	15	15	13	9
Mean Change in HBsAg (log_{10} IU/mL)	-1.89	-2.03	-2.55	-2.30

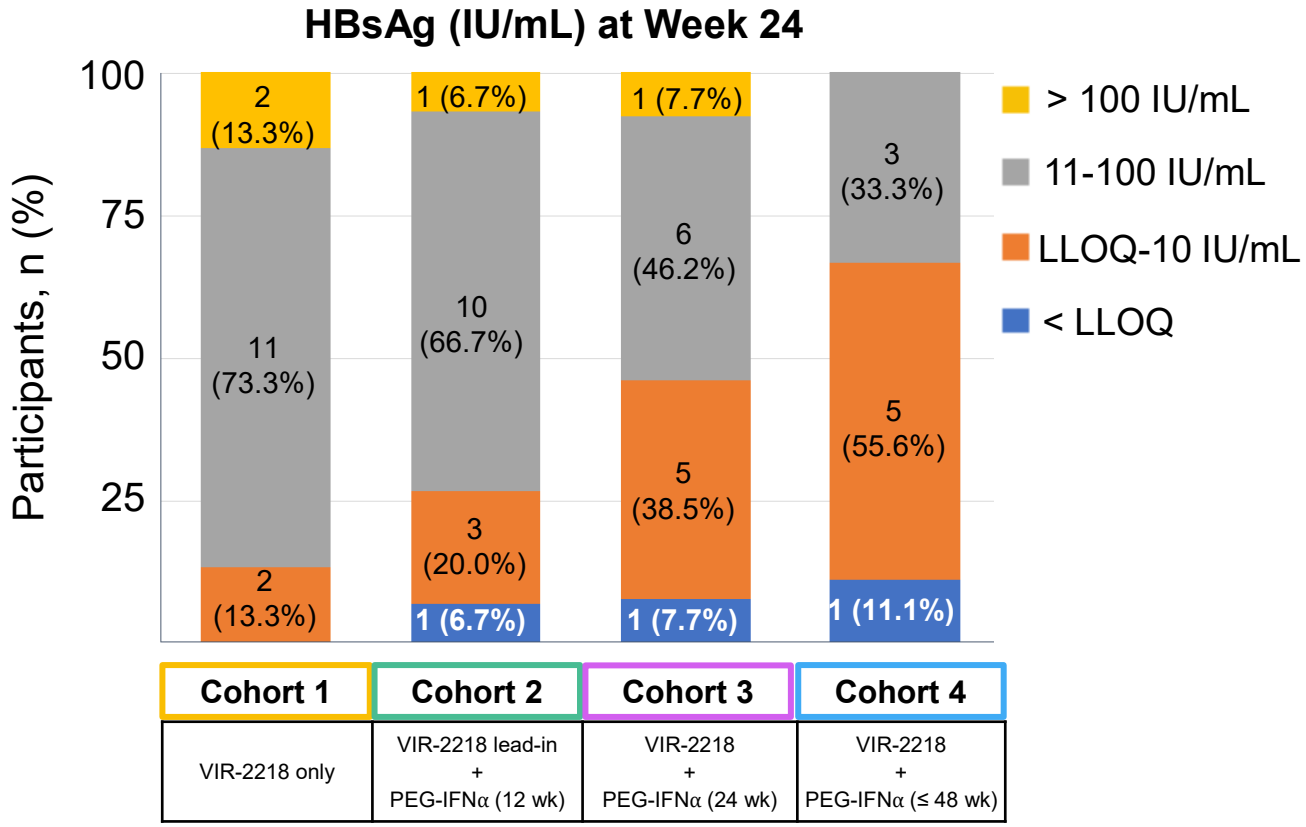
HBsAg change from baseline at Week 24 (log_{10} IU/mL)



*Participant achieved HBsAg < LLOQ (0.05 IU/mL).

HBeAg, hepatitis B e antigen; LLOQ, lower limit of quantitation; PEG-IFNα, peginterferon alfa-2a.

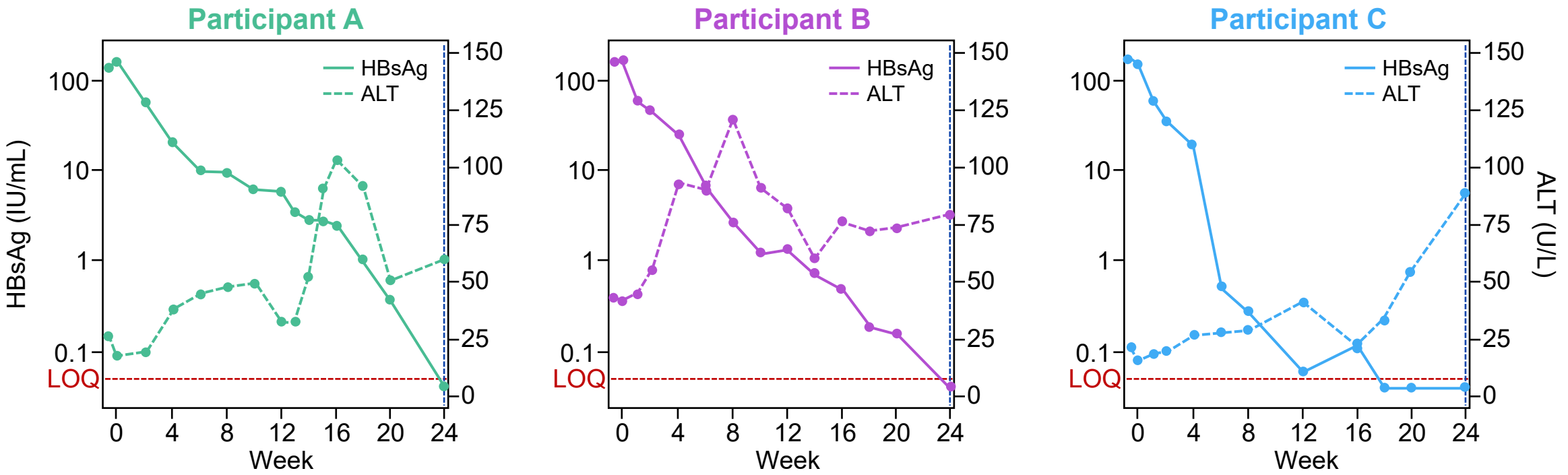
Majority of Participants Achieved HBsAg Levels Below 100 IU/mL at Week 24



- Across all cohorts, 48 of 52 (92%) participants who have completed the Week 24 visit achieved HBsAg < 100 IU/mL
- More participants receiving VIR-2218 concurrently initiated with PEG-IFNα (Cohorts 3 and 4; 12/22 [54.5%]) achieved HBsAg ≤ 10 IU/mL at Week 24, compared to those receiving VIR-2218 alone (Cohort 1; 2/15 [13.3%])
- Three participants achieved HBsAg < LLOQ by Week 24
  - Two of the 3 participants had anti-HBs seroconversion (one each in Cohorts 2 and 4)

Data include participants that have completed the Week 24 visit; HBsAg assay LLOQ and LLOD are 0.05 IU/mL.
anti-HBs, hepatitis B surface antibody; LLOD, lower limit of detection; LLOQ, lower limit of quantitation; PEG-IFNα, peginterferon alfa-2a.

Three Participants Achieved HBsAg < LLOQ by Week 24



Participant	A	B	C
Cohort	**2**	**3**	**4**
Age (years)	36	56	39
Gender	Male	Male	Male
Baseline HBeAg status	Negative	Positive[1]	Negative
Baseline HBsAg (IU/mL)	134	151	156
Anti-HBs at Week 24	Positive (130.6 mIU/mL)	Negative	Positive (84 mIU/mL)

[1]HBeAg at baseline was very low (0.16 IU/mL); the participant achieved HBeAg loss by Week 4.
HBsAg assay LLOQ and LLOD are 0.05 IU/mL; anti-HBs considered positive at > 10 mIU/mL.

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; anti-HBs, hepatitis B surface antibody; PEG-IFNα, peginterferon alfa-2a.

Summary of Results

- VIR-2218 alone or in combination with PEG-IFNα has been generally well tolerated
  - Majority of TEAEs have been Grade 1 or 2, with no treatment-related SAEs reported to date
- All VIR-2218 plus PEG-IFNα regimens were associated with clinically meaningful HBsAg reductions (> 2 $\log_{10}$ IU/mL on average) by Week 24
- Three participants receiving VIR-2218 and PEG-IFNα achieved HBsAg loss by Week 24; 2 of the 3 participants achieved anti-HBs seroconversion
- Concurrent initiation of VIR-2218 and PEG-IFNα therapy (Cohorts 3 and 4) resulted in the greatest HBsAg reductions compared to VIR-2218 alone or PEG-IFNα following a VIR-2218 lead-in
  - In Cohorts 3 and 4, most patients achieved HBsAg < 100 IU/mL and 55% achieved < 10 IU/mL at Week 24

PEG-IFNα, peginterferon alfa-2a; HBsAg, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody; TEAE, treatment-emergent adverse event.

Key Takeaways

- These data demonstrate that the antiviral activity of VIR-2218 can be potentiated by PEG-IFNα and support future evaluation of combination with novel immunomodulators
- Based on the proportion of participants achieving HBsAg < 10 IU/mL at Week 24, PEG-IFNα treatment for > 24 weeks may achieve higher rates of HBsAg loss
  - Cohort 4 is ongoing to evaluate PEG-IFNα treatment up to 48 weeks, with a target enrollment of 30 patients

PEG-IFNα, peginterferon alfa-2a; HBsAg, hepatitis B surface antigen

Acknowledgments

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