Safety, Tolerability, and Antiviral Activity of the siRNA VIR-2218 in Combination With the Investigational Neutralizing Monoclonal Antibody VIR-3434 For the Treatment of Chronic Hepatitis B Virus Infection: Preliminary Results From the Phase 2 MARCH Trial

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Disclosures

1. Dr. Edward Gane serves on HBV Scientific Advisory Boards for Gilead, ALIGOS, Janssen, Roche, and Assembly
2. He received unrestricted grant support from AbbVie for the Hepatitis C Test and Treat pilot study in Auckland, New Zealand
3. He is the Associate Editor of the *Journal of Hepatology*
4. He is a sponsored lecturer for the HCV Elimination Leaders Conference series for AbbVie

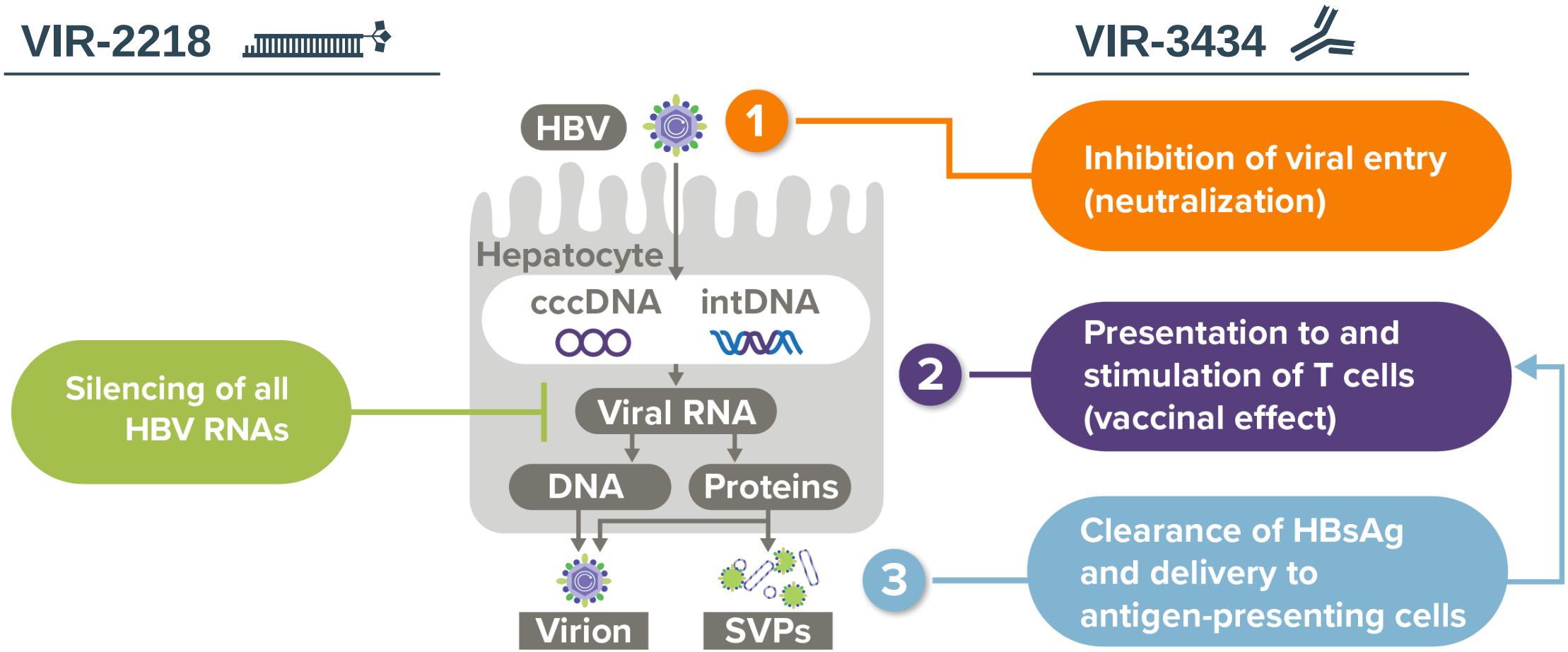
Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus.

Introduction

- There remains significant unmet medical need for a curative, well-tolerated chronic hepatitis B virus (HBV) treatment with a finite duration
- VIR-2218 is an investigational small interfering ribonucleic acid (siRNA) targeting the HBx region of the HBV genome[1]
- VIR-3434 is an investigational Fc-engineered human monoclonal antibody targeting the conserved antigenic loop of HBsAg[2]
- Here we report preliminary data from an ongoing trial evaluating the safety, tolerability, and antiviral activity of short-duration combination regimens of VIR-2218 and VIR-3434 in virally suppressed participants with chronic HBV infection

1. Lim Y-S, et al. *J Hepatol* 2022; 77(S1): S69; 2. Agarwal K, et al. *J Hepatol* 2022; 77(S1): S831.
Abbreviations: Fc, Fragment, crystallizable; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBx, hepatitis B virus X protein; siRNA, small interfering ribonucleic acid.

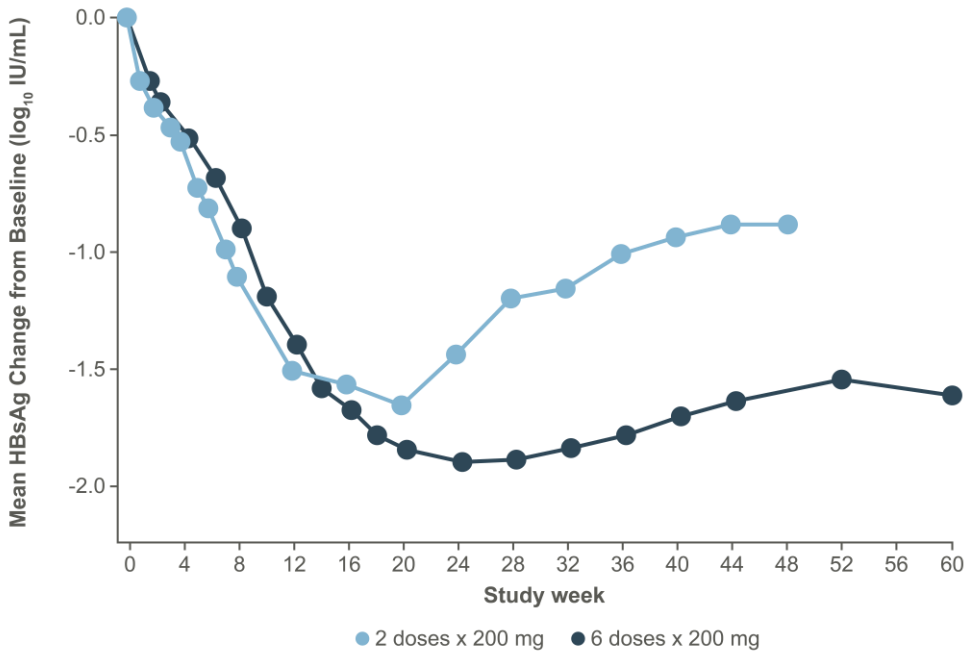
VIR-2218 and VIR-3434 Target Different Steps in the HBV Replication Cycle



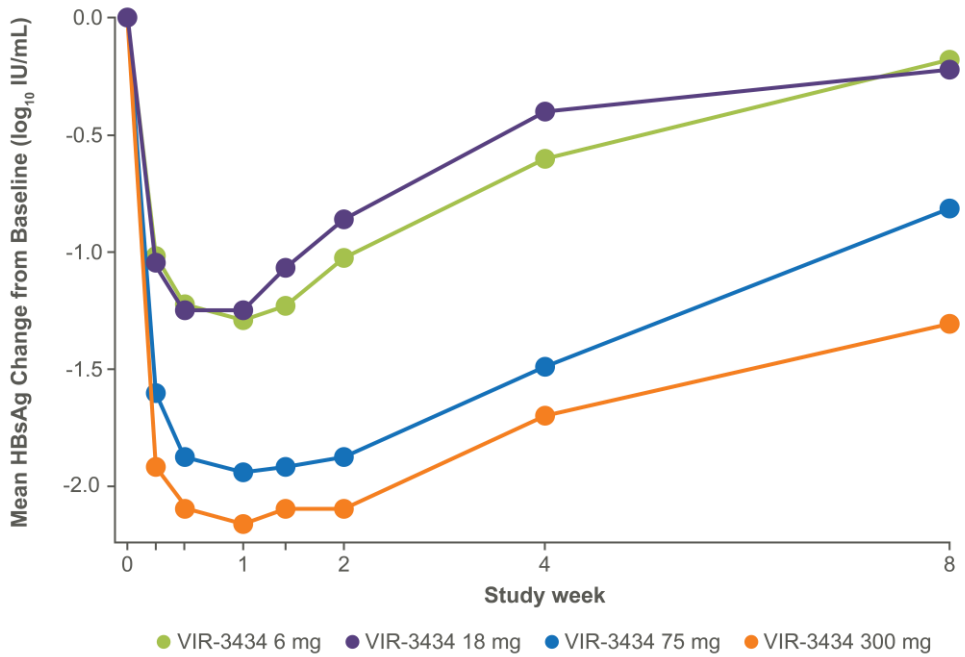
Abbreviations: cccDNA, covalently closed circular DNA; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; intDNA, integrated DNA; RNA, ribonucleic acid; SVPs, subviral particles.

VIR-2218 and VIR-3434 as Monotherapy Treatments Both Achieve HBsAg Reduction > 1 log_{10} IU/mL

VIR-2218 200 mg every 4 weeks for 2 vs. 6 doses achieves mean HBsAg reductions of 1.6 to 2.0 log_{10} IU/mL at nadir[1]

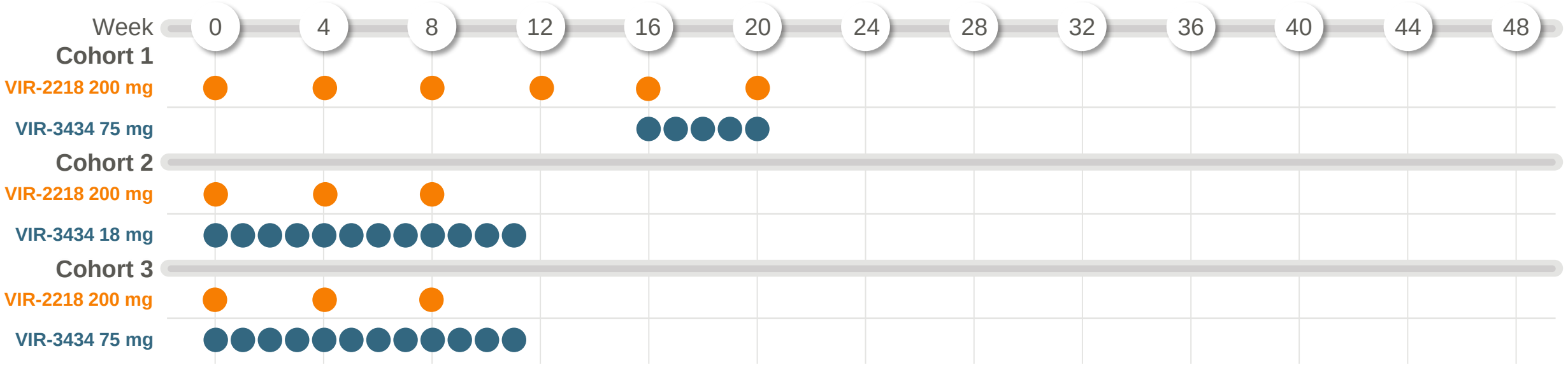


VIR-3434 single dose of 6 to 300 mg rapidly achieves mean HBsAg reductions of 1.3 to 2.2 log_{10} IU/mL at nadir[2]



1. Lim Y-S, et al. *J Hepatol* 2022; 77(S1): S69; 2. Agarwal K, et al. *J Hepatol* 2022; 77(S1): S831.
Abbreviations: HBsAg, hepatitis B surface antigen.

MARCH Study: Evaluating Combinations of VIR-2218 and VIR-3434



Study aims

- To evaluate the safety and tolerability of regimens containing VIR-2218 and VIR-3434
- To evaluate the efficacy of regimens containing VIR-2218 and VIR-3434

Primary endpoints

- Proportion of participants with treatment-emergent adverse events or serious adverse events
- HBsAg loss at end of treatment
- HBsAg loss at 24 weeks post-end of treatment

Secondary endpoints

- Proportion of participants with serum HBsAg < 10 IU/mL at end of treatment
- Absolute serum HBsAg and change from baseline

Abbreviations: HBsAg, hepatitis B surface antigen.

Key Inclusion/Exclusion Criteria

Inclusion

- Age 18-65 years
- Chronic HBV infection defined as a positive serum HBsAg, HBV DNA, or HBeAg on 2 occasions at least 6 months apart
- On NRTI therapy for ≥ 2 months
- HBV DNA < 100 IU/mL
- Cohorts 2 and 3 only: HBsAg < 3,000 IU/mL

Exclusion

- Significant fibrosis or cirrhosis (FibroScan > 8.5 kPa at screening or Metavir F3/F4 liver biopsy within 1 year)
- Direct bilirubin or INR > ULN
- ALT or AST > 3 x ULN
- Coinfection with HIV, HCV, or hepatitis Delta
- Immunosuppressive therapy

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

MARCH: Demographics and Baseline Characteristics

	Cohort 1 N=17	Cohort 2 N=4	Cohort 3 N=19
Median age (range)	51.0 (26–64)	49.0 (47–50)	48.0 (34–63)
Sex, n (%)			
Male	12 (70.6)	4 (100.0)	11 (57.9)
Female	5 (29.4)	0	8 (42.1)
Race, n (%)			
Asian	1 (5.9)	0	12 (63.2)
Native Hawaiian or Other Pacific Islander	2 (11.8)	2 (50.0)	2 (10.5)
White	12 (70.6)	1 (25.0)	5 (26.3)
Other	2 (11.8)	1 (25.0)	0
BMI (kg/m^2), median (range)	25.8 (19.6–34.1)	27.4 (21.2–33.9)	24.1 (18.7–34.5)
Baseline HBsAg Levels (IU/mL), median (range)	4,270.5 (759.7–16,294.3)	1,901.2 (33.1–3,977.4)	1,098.4 (83.2–3,241.2)
Baseline HBsAg Levels, n (%)			
≥ 10,000 IU/mL	3 (17.6)	0	0
1,000 - < 10,000 IU/mL	13 (76.5)	3 (75.0)	10 (52.6)
100 - < 1,000 IU/mL	1 (5.9)	0	7 (36.8)
< 100 IU/mL	0	1 (25.0)	2 (10.5)
HBeAg Status at Baseline			
Negative	16 (94.1)	3 (75.0)	16 (84.2)
Positive	1 (5.9)	1 (25.0)	3 (15.8)

Abbreviations: BMI, body mass index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

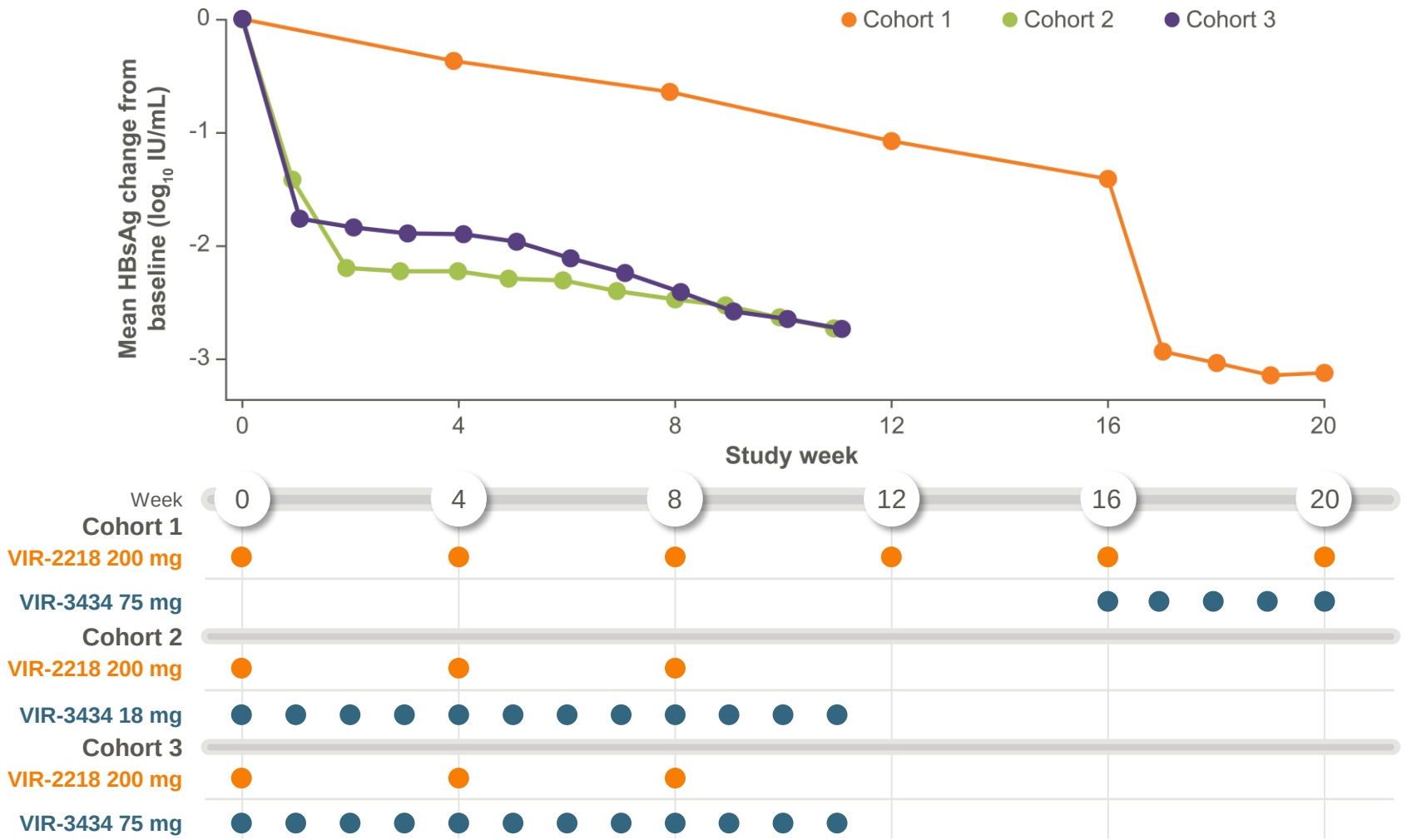
Combination Treatment with VIR-2218 and VIR-3434 Was Generally Well Tolerated

	Cohort 1 N=17	Cohort 2 N=4	Cohort 3 N=19
Any AE, n (%)	4 (23.5)	2 (50.0)	9 (47.4)
Grade 1	1 (5.9)	2 (50.0)	8 (42.1)
Grade 2	3 (17.6)	0	1 (5.3)
Treatment-related	0	0	2 (10.5)
SAE, n	0	0	0
AE Leading to Study Drug Discontinuation, n	0	0	0
Study Discontinuations, n	0	0	0
ALT elevations, n (%)			
Grade 1	5 (29.4)	0	10 (52.6)
Grade 2	1 (5.9)	0	0

- **All AEs were mild or moderate; no AEs led to treatment discontinuation**
- **Treatment-related AEs of malaise and myalgia (n=1) and injection-site pain (n=1) were reported**
  - All were grade 1 and resolved on treatment

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event.

VIR-2218 Plus VIR-3434 Achieved Mean HBsAg Reductions > 2.5 log_{10} IU/mL at End of Treatment



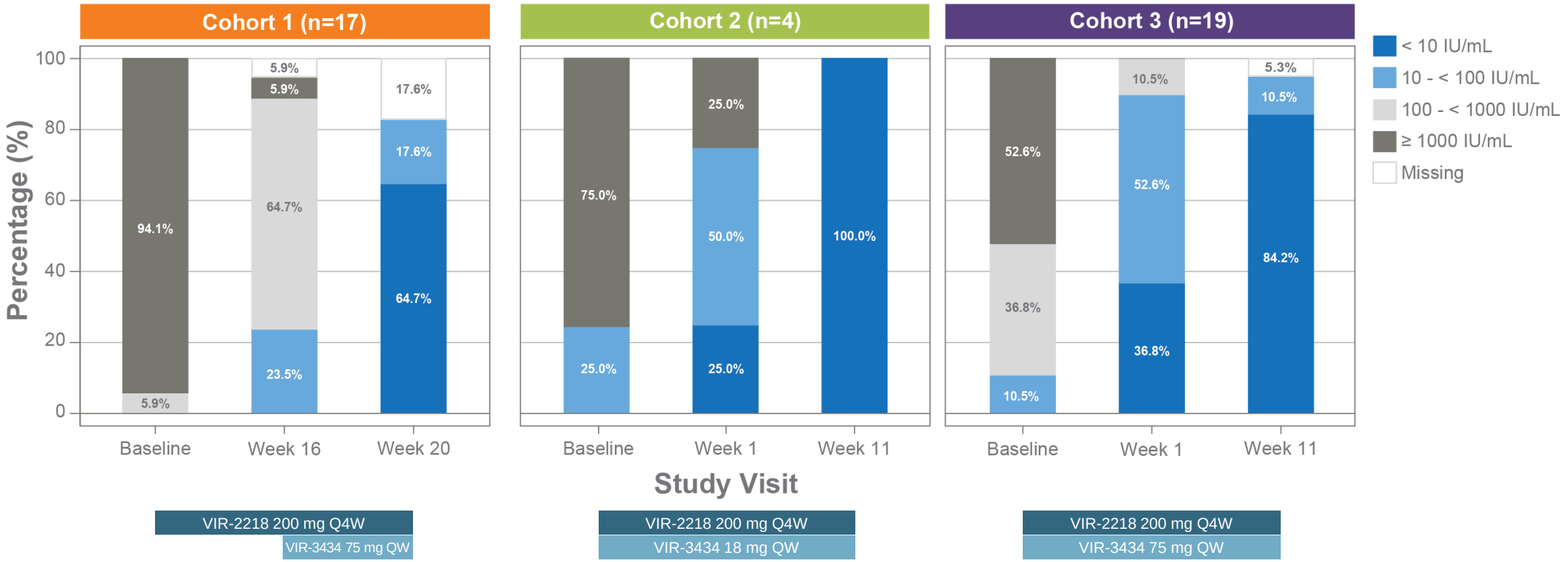
Mean (SD) HBsAg Change from Baseline at End of Treatment (log_{10} IU/mL)

Cohort 1	-3.1 (0.4)
Cohort 2	-2.7 (0.3)
Cohort 3	-2.7 (0.6)

- HBsAg kinetics demonstrate additive reductions from VIR-2218 and VIR-3434
- All participants achieved > 1.5 log_{10} IU/mL reductions from baseline HBsAg at end of treatment

Abbreviations: HBsAg, hepatitis B surface antigen; SD, standard deviation.

Most Participants Achieved HBsAg < 10 IU/mL at End of Treatment



⬡ No participants achieved HBsAg loss at end of treatment

Abbreviations: HBsAg, hepatitis B surface antigen; QW, every week; Q4W, every 4 weeks.

Summary of Results

- VIR-2218 and VIR-3434 combination regimens up to 20 weeks were generally well tolerated and associated with mostly mild adverse events
- VIR-2218 and VIR-3434 combination regimens achieved mean HBsAg reductions > 2.5 $\log_{10}$ IU/mL in all cohorts, and absolute HBsAg levels < 10 IU/mL were achieved in most participants
- Patterns of response demonstrate additive HBsAg reduction from the complementary modes of action of VIR-2218 and VIR-3434

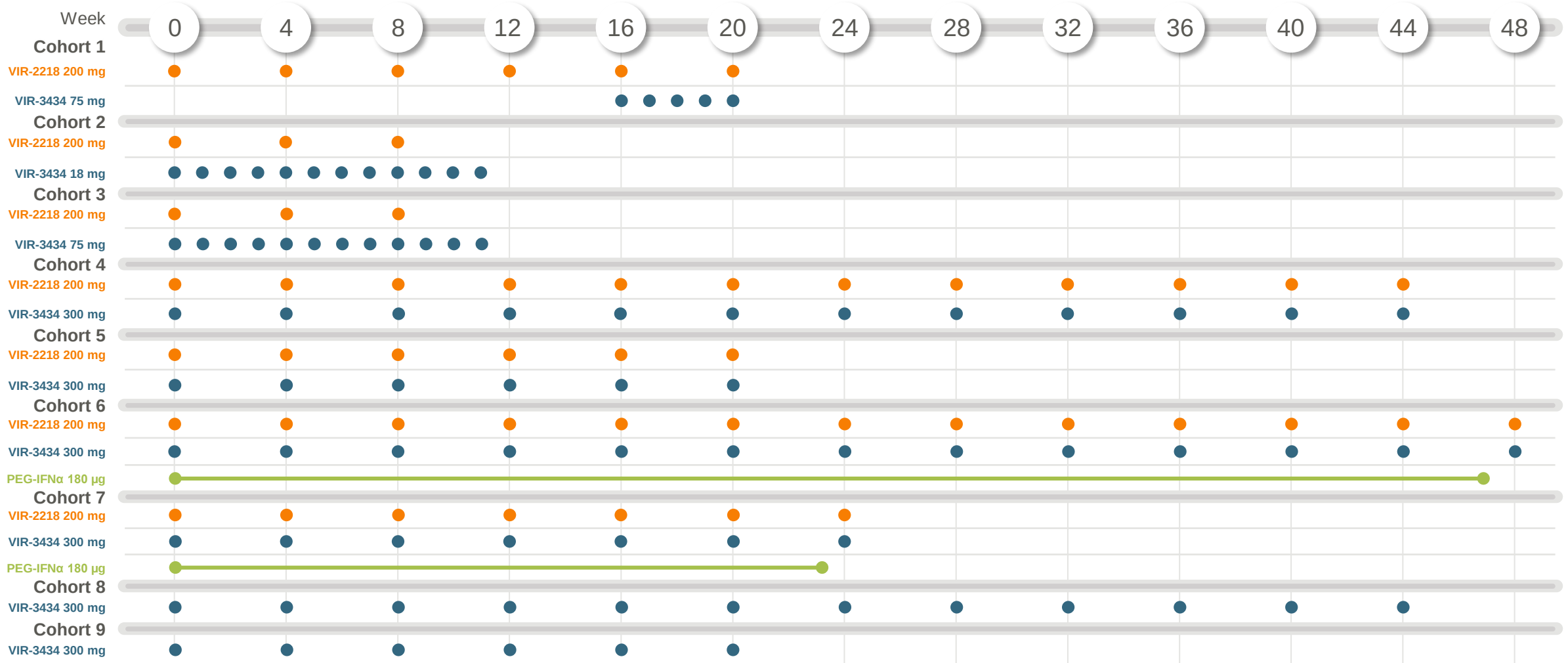
Abbreviations: HBsAg, hepatitis B surface antigen.

Key Takeaways

- The HBsAg declines achieved with the combination of VIR-2218 plus VIR-3434 are among the largest seen to date with novel HBV therapies
- These data support the continued evaluation of combination regimens containing VIR-2218 and VIR-3434 for the functional cure of chronic HBV infection
- Patterns of response suggest that longer durations of treatment may achieve additional reduction in HBsAg
- Cohorts evaluating longer durations of treatment with VIR-2218 plus VIR-3434 or VIR-3434 monotherapy, as well as regimens evaluating the addition of interferon, are currently recruiting in this ongoing trial (NCT04856085)

Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

MARCH Study: Evaluating Combinations of VIR-2218, VIR-3434, and/or PEG-IFNα



Abbreviations: PEG-IFNα, pegylated interferon alfa-2a.

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