Safety and Antiviral Activity of Short-duration Combinations of the Investigational Small Interfering Ribonucleic Acid VIR-2218 With the Neutralizing, Vaccinal Monoclonal Antibody VIR-3434: Post-treatment Follow Up From the Phase 2 MARCH Trial

Edward Gane[1], Alina Jucov[2], Marta Dobryanska[3], Ki Tae Yoon[4], Tien-Huey Lim[5], Andre Arizpe[6], Daniel Cloutier[6], Michael A. Chattergoon[6], Shenghua Mao[6], Sneha V. Gupta[6], Gregory Camus[6], Carey Hwang[6], Young-Suk Lim[7]

[1]Faculty of Medicine, University of Auckland, Auckland, New Zealand; [2]Arensia Exploratory Medicine GmbH, Düsseldorf, Germany and Nicolae Testemitanu State University of Medicine and Pharmacy, Chişinău, Moldova; [3]Medical Center of Limited Liability Company "Harmoniya krasy" and Arensia Exploratory Medicine, Kyiv, Ukraine; [4]Pusan National University Yangsan Hospital, Pusan National University College of Medicine, Yangsan, Korea; [5]Department of Gastroenterology, Middlemore Hospital, Auckland, New Zealand; [6]Vir Biotechnology, Inc., San Francisco, CA; [7]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

European Association for the Study of Liver (EASL), EASL Congress; 21–24 June 2023; Vienna, Austria. Presentation OS-031

Edward Gane, MBChB, MD, FRACP, MNZM

Dr. Gane is Professor of Medicine at the University of Auckland, and Chief Hepatologist, Transplant Physician, and Deputy Director of the New Zealand Liver Transplant Unit at Auckland City Hospital, Auckland, New Zealand

He is an investigator for many international clinical trials of therapies for chronic viral hepatitis with particular interest in early-phase development of new direct-acting antiviral therapies against hepatitis C and hepatitis B

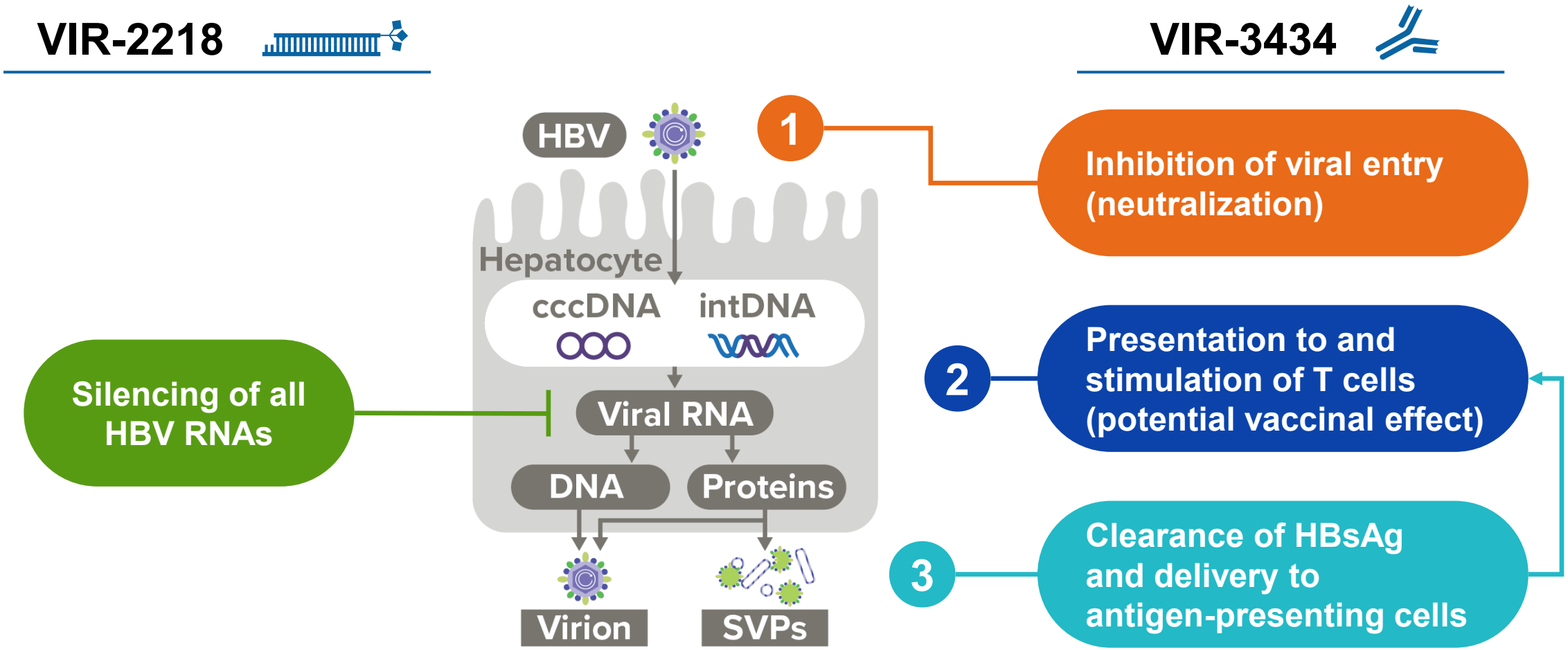
Dr. Gane has published over 500 papers in peer-reviewed journals and is an associate editor for the *Journal of Hepatology*

Introduction

- There is significant unmet medical need for a curative, well-tolerated, chronic HBV treatment with a finite duration
- VIR-2218 is an investigational 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]
- When administered together, VIR-2218 and VIR-3434 are associated with favorable safety and tolerability and substantial reductions in serum HBsAg[3]
- Here, we report the post-treatment data from Part A of the MARCH trial, evaluating short durations of combination therapy of VIR-2218 and low-dose VIR-3434 in virally suppressed participants with chronic HBV infection

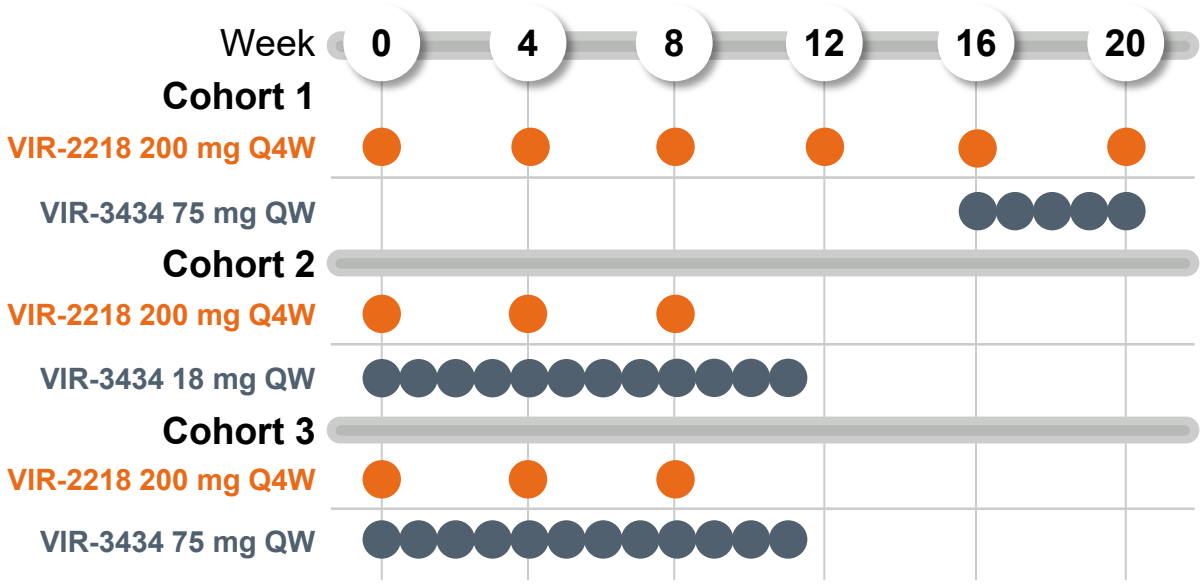
1. Lim Y-S, et al. J Hepatol 2022; 77(S1): S69; **2.** Agarwal K, et al. J Hepatol 2022; 77(S1): S831; **3.** Gane E, et al. J Hepatol 2022; 76(S1): S18.
Abbreviations: Fc, fragment, crystallizable; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBx, hepatitis B virus X protein; siRNA, small interfering ribonucleic acid.

VIR-2218 and VIR-3434 Target Different Steps in the HBV Replication Cycle[1]



1. Lempp FA, Volz T, Cameroni E, et al. 2022. doi: 10.1101/2022.09.09.507326.
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.

MARCH Part A: Preliminary Low-Dose, Short-Duration Regimens of VIR-2218 Plus VIR-3434



- Part A cohorts were designed to rapidly assess the safety and potential additive antiviral activity of VIR-2218 plus VIR-3434
- Lead-in and simultaneous treatment approaches were evaluated to assess the contribution of each component
- Enrollment in cohort 2 was limited due to emerging phase 1 data enabling evaluation of higher VIR-3434 dose levels

Abbreviations: QW, once weekly; Q4W, once every 4 weeks.

Key Inclusion/Exclusion Criteria

Inclusion

- Age 18 to 65 years (inclusive)
- 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 HDV
- 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; 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 = 17	Cohort 2 n = 4	Cohort 3 n = 19
Age (years), median (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)	1 (25.0)	12 (63.2)
Native Hawaiian or Other Pacific Islander	1 (5.9)	2 (50.0)	2 (10.5)
White	12 (70.6)	1 (25.0)	5 (26.3)
Other	3 (17.6)	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 (log_{10} IU/mL), median (range)	3.63 (2.88, 4.21)	3.26 (1.52, 3.60)	3.04 (1.92, 3.51)
Baseline HBsAg, n (%)			
≥10,000 IU/mL	3 (17.6)	0	0
1,000 to <10,000 IU/mL	13 (76.5)	3 (75.0)	10 (52.6)
100 to <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.

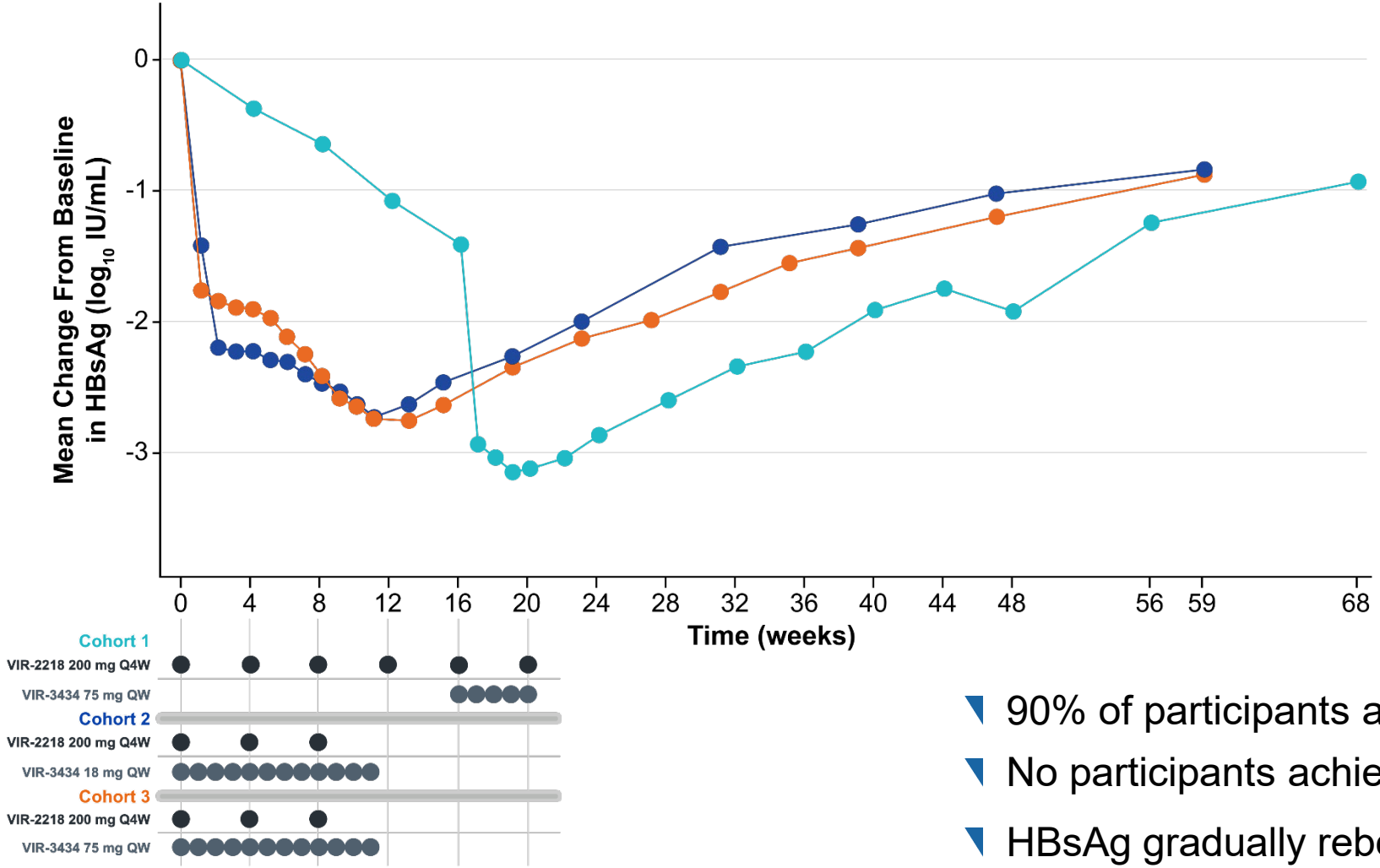
Combination Treatment With VIR-2218 and VIR-3434 Was Generally Well Tolerated

Participants	Cohort 1 n = 17	Cohort 2 n = 4	Cohort 3 n = 19
Any TEAE, n (%)	6 (35.3)	2 (50.0)	13 (68.4)
Grade 1	0	1 (25.0)	6 (31.6)
Grade 2	5 (29.4)	1 (25.0)	5 (26.3)
Grade 3	1 (5.9)	0	2 (10.5)
Treatment-related TEAE	0	0	2 (10.5)[a]
SAE, n	0	0	0
TEAE leading to study drug discontinuation, n	0	0	0
Study discontinuations, n	0	0	0
ALT elevations, n (%)			
Grade 1	5 (29.4)	1 (25.0)	12 (63.2)
Grade 2	0	0	1 (5.3)
Grade 3[b]	1 (5.9)	0	1 (5.3)
Grade 4[b]	1 (5.9)	0	0

- Most TEAEs were mild to moderate
- All treatment-related TEAEs were grade 1
- ALT elevations were asymptomatic, and markers of liver function were stable

[a]Malaise and myalgia (n = 1); injection site pain (n = 1). [b]The grade 4 ALT elevation and one of the grade 3 ALT elevations were associated with HBV DNA elevations following NRTI discontinuation; the other grade 3 ALT elevation occurred after end of treatment in a participant who reported heavy alcohol consumption.
TEAE defined as any AE that increased in severity or that was newly developed at or after initial dosing of study drug
Abbreviations: TEAE, treatment emergent adverse event; ALT, alanine aminotransferase; SAE, serious adverse event.

VIR-2218 Plus VIR-3434 Maintained Mean HBsAg Reductions From Baseline of Almost 1 Log_{10} IU/mL for 48 Weeks Post-EOT



Mean (SD) HBsAg Change from baseline (log_{10} IU/mL)

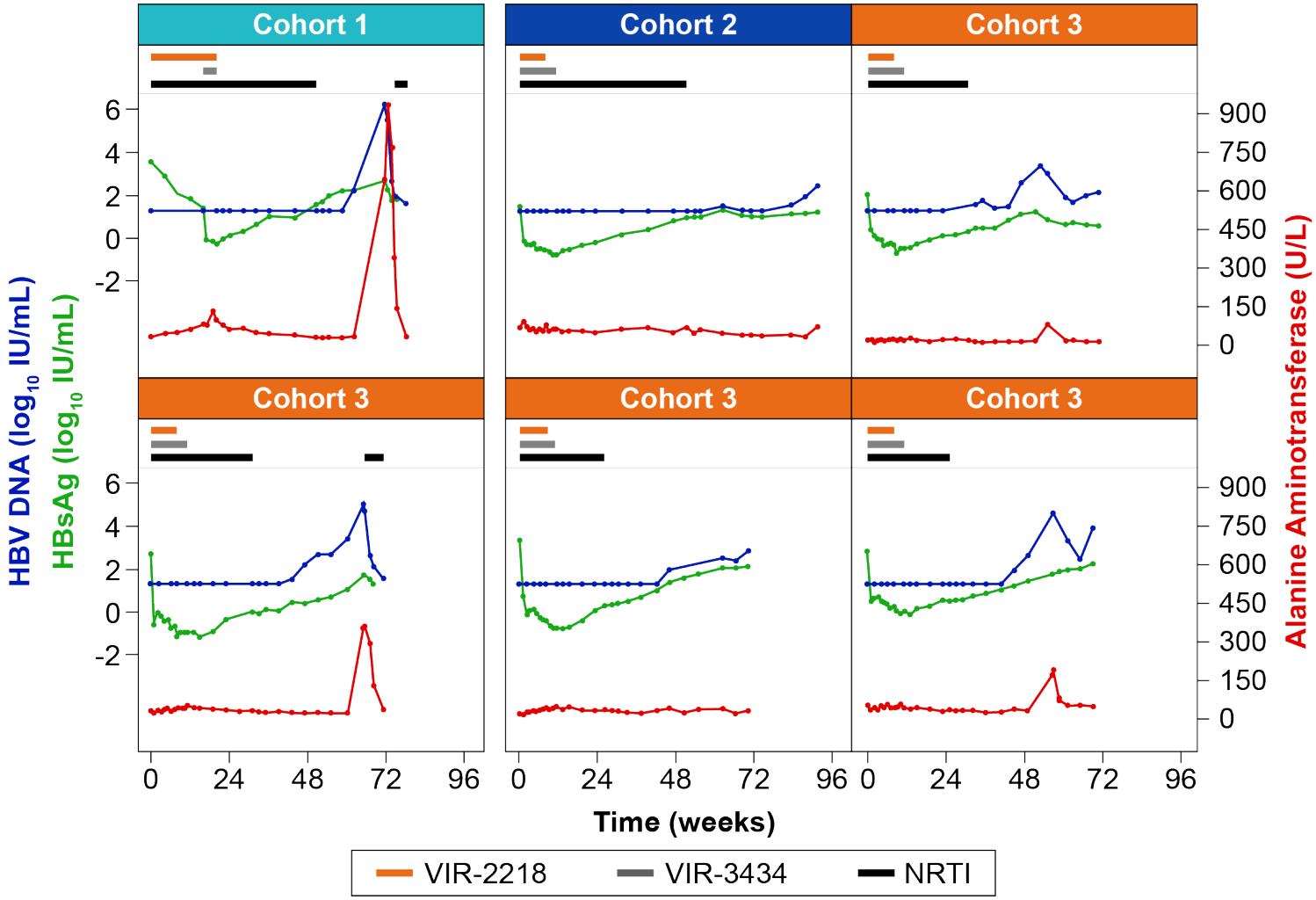
	EOT	24 Weeks Post-EOT	48 Weeks Post-EOT
Cohort 1	-3.1 (0.4)	-1.7 (0.53)	-0.9 (0.41)
Cohort 2	-2.7 (0.3)	-1.3 (0.55)	-0.8 (0.62)
Cohort 3	-2.7 (0.6)	-1.5 (0.35)	-0.9 (0.35)

- 90% of participants achieved HBsAg <10 IU/mL by EOT
- No participants achieved HBsAg seroclearance
- HBsAg gradually rebounded after EOT in all cohorts

Abbreviations: EOT, end of treatment; HBsAg, hepatitis B surface antigen; SD, standard deviation.

Majority of Participants Who Discontinued NRTIs Remain Off NRTI Therapy

- The majority of participants met criteria for NRTI discontinuation:
  - HBsAg <100 IU/mL and ≥1 log_{10} IU/mL reduction from baseline HBsAg level
  - HBV DNA <LLOQ
  - HBeAg-negative
  - ALT ≤2 x ULN
- A subset of participants (n = 6) discontinued NRTI therapy[a]
- 4/6 participants remained off NRTI therapy as of the last available follow up
- 2/6 participants experienced HBV DNA and ALT increases, and restarted NRTI therapy



[a]Due to changes in NRTI discontinuation eligibility requirements in a protocol amendment, most participants who met NRTI discontinuation criteria remained on NRTIs.
Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantitation; NRTI, nucleos(t)ide reverse transcriptase inhibitor; ULN, upper limit of normal.

Summary of Results

- The combination of VIR-2218 plus low-dose VIR-3434 was generally well tolerated; reported adverse events were generally mild with no discontinuations from treatment
- When co-administered for 5 or 12 weeks, VIR-2218 and VIR-3434 were associated with a 2.7 to 3.1 $\log_{10}$ IU/mL reduction in HBsAg, with 90% of participants achieving HBsAg <10 IU/mL by end of treatment
- HBsAg rebounded after treatment but remained almost 1 $\log_{10}$ IU/mL below baseline at 48 weeks after the end of treatment
- Among a small subset of participants who discontinued NRTI therapy, most remain off-treatment

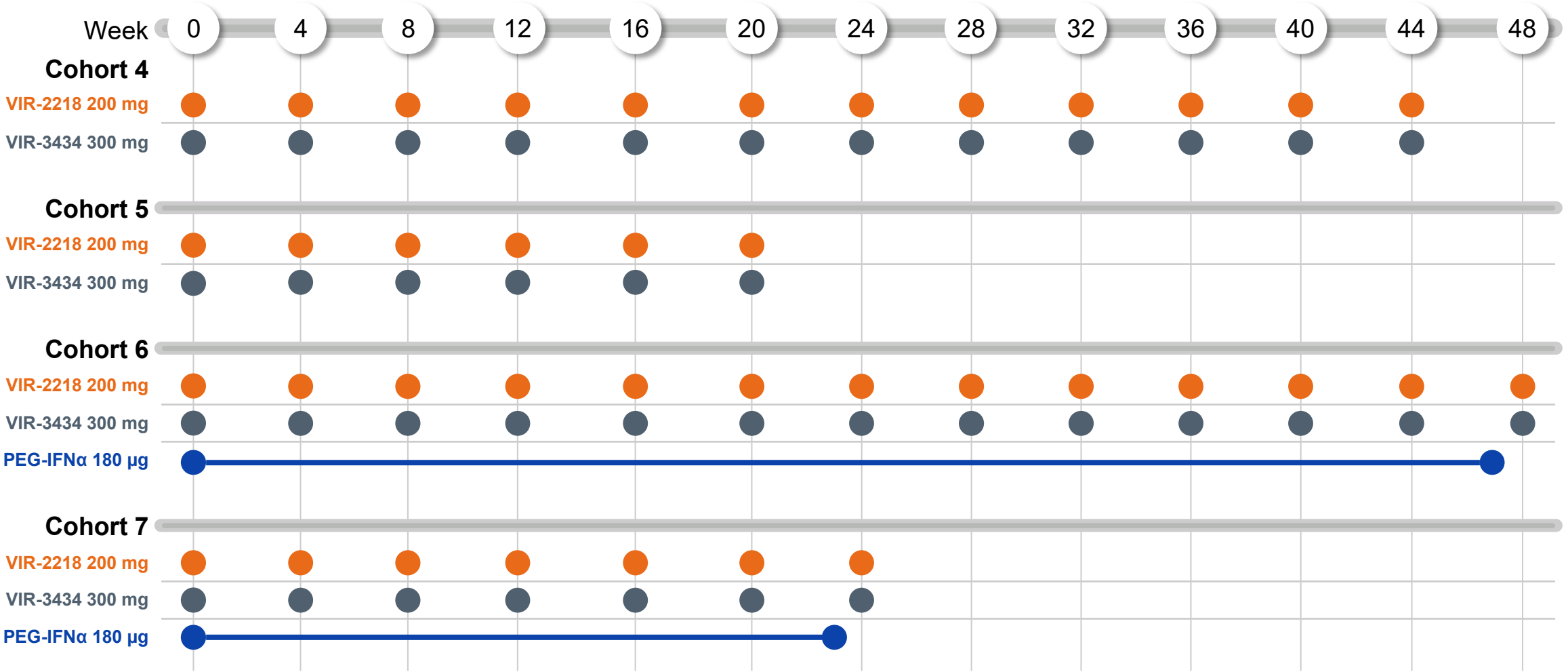
Abbreviations: HBsAg, hepatitis B surface antigen; NRTI, nucleos(t)ide reverse transcriptase inhibitor.

Key Takeaways

- Part A of the MARCH study successfully established proof-of-concept for the combination of VIR-2218 plus VIR-3434: low-dose, short-duration regimens were well tolerated and resulted in additive antiviral activity
- These data, together with VIR-2218 plus PEG-IFNα data showing 31% HBsAg seroclearance at end of treatment,[1] support the evaluation of longer durations of VIR-2218 plus VIR-3434 with and without PEG-IFNα in Part B of the MARCH study

1. Yuen et al. Hepatology 2022; 76(S1):S18.
Abbreviations: HBsAg, hepatitis B surface antigen; PEG-IFNα, pegylated interferon alfa-2a.

MARCH Part B: Ongoing Cohorts Evaluating Combinations of VIR-2218, VIR-3434, and/or PEG-IFNα



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

Acknowledgements

We thank the study participants, site coordinators, and study investigators, especially those impacted by the ongoing conflict in Ukraine.

This study is being funded by Vir Biotechnology, Inc.

Canada
Brian Conway, Vancouver ID Research and Care Centre Society
Jordan Feld, Toronto Centre For Liver Disease
Magdy Elkhashab, Toronto Liver Centre

Germany
Christoph Antoni, Universitatsmedizin Mannheim (UMM)
Eugen Zizier, Universitatsklinikum Ulm
Heiner Wedemeyer, Medizinische Hochschule Hannover
Kathrin Sprinzl, Medizinische Klinik I

Hong Kong
Grace Wong, Prince of Wales Hospital
Man-Fung Yuen, Queen Mary Hospital
Wai-man Yip, Alice Ho Miu Ling Nethersole Hospital

Malaysia
Haniza BT Omar, Hospital Selayang
Rosaida BT Mohd Said, Hospital Serdang
Ruveena Bhavani K N Rajaram, University Malaya Medical Centre

Moldova
Alina Jucov, ICS ARENSIA Exploratory Medicine SRL

New Zealand
Dean Quinn, P3 Research Wellington
Edward Gane, Auckland Clinical Studies
Richard Stubbs, P3 Research Tauranga
Tien-Huey Lim, Middlemore Hospital

Romania
Anca Sreinu Cercel, ARENSIA Exploratory Medicine Research Clinic, National Institute of Infectious Diseases “Matei Bals”

South Korea
Jung-hwan Yoon, Seoul National University Hospital
Ki-Tae Yoon, Pusan National University Yangsan Hospital
Won Young Tak, Kyungpook National University Hospital
Young Suk Lim, Asan Medical Center

Taiwan
Chao-Wei Hsu, Chang Gung Memorial Hospital - Linkou
Chi-Yi Chen, Ditmanson Medical Foundation Chia-Yi Christian Hospital
Chun-Jen Liu, National Taiwan University Hospital
Sheng-Shun Yang, Taichung Veterans General Hospital
Tsung-Hui Hu, Chang Gung Memorial Hospital - Kaohsiung
Wan-Long Chuang, Kaohsiung Medical University Hospital

Ukraine
Marta Dobryanska, ARENSIA Exploratory Medicine Research Clinic Harmoniya Krasy Medical Center

United Kingdom
Alison Uriel, North Manchester General Hospital
David Mutimer, UHB NHS Foundation Trust, Queen Elizabeth Hospital
Kosh Agarwal, King’s College Hospital
Patrick Kennedy, Barts Liver Centre

United States
Eugene Schiff, University of Miami
Federico Hinestrosa, Orlando Immunology Center
Jennifer Price, University of California San Francisco
Mark Sulkowski, Johns Hopkins University
Ronald Nahass, ID Care Inc.

Editorial support was provided by Oxford PharmaGenesis Inc., Newtown, PA, USA; and funded by Vir Biotechnology, Inc.