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


**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

VIR-2218

Silencing of all HBV RNAs

1. Inhibition of viral entry (neutralization)

VIR-3434

2. Presentation to and stimulation of T cells (vaccinal effect)

3. Clearance of HBsAg and delivery to antigen-presenting cells

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


**Abbreviations:** HBsAg, hepatitis B surface antigen.

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

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
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

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 N=17</th>
<th>Cohort 2 N=4</th>
<th>Cohort 3 N=19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
<td>51.0 (26–64)</td>
<td>49.0 (47–50)</td>
<td>48.0 (34–63)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (70.6)</td>
<td>4 (100.0)</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (29.4)</td>
<td>0</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5.9)</td>
<td>0</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>2 (11.8)</td>
<td>2 (50.0)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>White</td>
<td>12 (70.6)</td>
<td>1 (25.0)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (11.8)</td>
<td>1 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td><strong>BMI (kg/m²), median (range)</strong></td>
<td>25.8 (19.6–34.1)</td>
<td>27.4 (21.2–33.9)</td>
<td>24.1 (18.7–34.5)</td>
</tr>
<tr>
<td><strong>Baseline HBsAg Levels (IU/mL), median (range)</strong></td>
<td>4,270.5 (759.7–16,294.3)</td>
<td>1,901.2 (33.1–3,977.4)</td>
<td>1,098.4 (83.2–3,241.2)</td>
</tr>
<tr>
<td><strong>Baseline HBsAg Levels, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10,000 IU/mL</td>
<td>3 (17.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1,000 - &lt; 10,000 IU/mL</td>
<td>13 (76.5)</td>
<td>3 (75.0)</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td>100 - &lt; 1,000 IU/mL</td>
<td>1 (5.9)</td>
<td>0</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>&lt; 100 IU/mL</td>
<td>0</td>
<td>1 (25.0)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td><strong>HBeAg Status at Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16 (94.1)</td>
<td>3 (75.0)</td>
<td>16 (84.2)</td>
</tr>
<tr>
<td>Positive</td>
<td>1 (5.9)</td>
<td>1 (25.0)</td>
<td>3 (15.8)</td>
</tr>
</tbody>
</table>

**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

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

- 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

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 greater than 2.5 log₁₀ IU/mL in all cohorts, and absolute HBsAg levels less than 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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