Vesatolimod (GS-9620) Is Safe and Pharmacodynamically Active in HIV-Infected Individuals

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Disclosures

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Immune-Based Strategies to Eliminate HIV Reservoirs

- **Protect ART**
- **Activate**
- **Eliminate**

**Goal**
Combine TLR7 agonist, bNAb, therapeutic vaccine

**Infected CD4 T cells**

**Vesatolimod (TLR7 agonist)**

**Protect ART**

**Recruit immune cells**

**Vaccines**

**bNAb**

**NK cells**

**MΦs**

**T cells**

ART, antiretroviral therapy; bNAb, broadly neutralizing antibody; MΦs, macrophages; NK, natural killer; TLR7, toll-like receptor-7.
Proof of Concept in Nonhuman Primate Model

**TLR7 + bNAb**

5/11 No Rebound

**TLR7 + Vaccine**

3/9 Controllers

Log SIV RNA Copies/mL

Days following ART discontinuation

Log SHIV RNA Copies/mL

Days following ART discontinuation


SHIV, simian/human immunodeficiency virus; SIV, simian immunodeficiency virus.
Vesatolimod Dose Escalation Study in PLWH

**Key inclusion criteria:**
- CD4 count ≥400 cells/μL
- HIV-1 RNA levels <50 copies/mL x ≥1 year
- Pre-ART CD4 nadir ≥200 cells/μL

**Objectives:**
- Safety, PK
- PD parameters:
  - ISG, cytokines, cell activation
- Virology:
  - Plasma HIV RNA

**PLWH on ART**
N=48

Randomized 6:2
VES:PBO
PO, fasted
Every other week

1 mg x 6
2 mg x 6
4 mg x 6
6 mg x 10
8 mg x 10
10 mg x 3 → 12 mg x 7 doses

NCT02858401
PLWH: People Living with HIV; ISG, interferon-stimulated gene; PBO, placebo; PD, pharmacodynamics; PK, pharmacokinetics; VES, vesatolimod.
Overall Safety

- 1 Grade 3 AE (abdominal pain) and 1 serious AE (diverticulitis; 2 mg cohort)
  - Both unrelated to study drug and occurring in same participant
- No discontinuations due to AEs; no Grade 4 AEs; no deaths

<table>
<thead>
<tr>
<th>Participants, n (%)</th>
<th>PBO n=12</th>
<th>1 mg n=6</th>
<th>2 mg n=6</th>
<th>4 mg n=6</th>
<th>6 mg n=6</th>
<th>8 mg n=6</th>
<th>10/12 mg n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade AE</td>
<td>9 (75)</td>
<td>4 (67)</td>
<td>4 (67)</td>
<td>2 (33)</td>
<td>4 (67)</td>
<td>5 (83)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (17)</td>
<td>3 (50)</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>2 (33)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Study drug-related AE</td>
<td>2 (17)</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>3 (50)</td>
<td>3 (50)</td>
</tr>
</tbody>
</table>
## Common Adverse Events (> 1 participant by cohort)

<table>
<thead>
<tr>
<th>Participants, n (%)</th>
<th>PBO n=12</th>
<th>1 mg n=6</th>
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<th>4 mg n=6</th>
<th>6 mg n=6</th>
<th>8 mg n=6</th>
<th>10/12 mg n=6</th>
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</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>9 (75)</td>
<td>4 (67)</td>
<td>4 (67)</td>
<td>2 (33)</td>
<td>4 (67)</td>
<td>5 (83)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (25)</td>
<td>1 (17)</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (17)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (25)</td>
<td>2 (33)</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>0</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (8)</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Myaligia</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Sinus Congestion</td>
<td>1 (8)</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>URI</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
</tbody>
</table>

URI: upper respiratory tract infection
NK Cell Activation

1st administration at each dose level shown

- Similar trends observed in CD4 and CD8 T lymphocytes
Circulating Cytokines

IL-1RA, interleukin 1 receptor antagonist; IP-10, IFN gamma-induced protein 10; ITAC, IFN-inducible T-cell-α chemoattractant
Induction of ISG15 mRNA

<table>
<thead>
<tr>
<th>ISG15 fold change (by cohort)</th>
<th>Participants, n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/12 mg</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>8 mg</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>6 mg</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>4 mg</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>2 mg</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>1 mg</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Placebo</td>
<td>1 2 3 4 5 6</td>
</tr>
</tbody>
</table>

White cells are missing data

ISG, Interferon-stimulated gene
Virologic Results

<table>
<thead>
<tr>
<th>PBO</th>
<th>1 mg n=6</th>
<th>2 mg n=6</th>
<th>4 mg n=6</th>
<th>6 mg n=6</th>
<th>8 mg n=6</th>
<th>10/12 mg n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pVL &gt; 20 copies/mL, n</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>pVL range, copies/mL</td>
<td>21-2430</td>
<td>21–42</td>
<td>21</td>
<td>23–69</td>
<td>32</td>
<td>-</td>
</tr>
</tbody>
</table>

- Most occurrences of plasma viral load elevations > 20 copies/mL were isolated
- No evidence of changes in plasma HIV RNA by single copy assay, or in total cell-associated HIV DNA or HIV RNA

pVL, plasma viral load.
Conclusions

♦ In this placebo controlled, phase 1 study in PLWH:
  – Multiple doses of VES 1-12 mg were well tolerated
  – Plasma exposure of VES was generally dose proportional
  – Immune stimulation was evident at ≥ 6 mg doses
    • Cellular activation markers, plasma cytokine increases and ISG mRNA induction
  – No obvious changes in virologic markers

♦ Trials evaluating the efficacy of VES, alone and in combination with other agents, are in progress
Acknowledgments

We extend our thanks to the study participants and investigators.

This study was funded by Gilead Sciences Inc.
Back-up Slides
Vesatolimod Dose Escalation: Design and Assessments

Week 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

VES Dosing:
+ ART
VES 1, 2, 4 mg x 6 doses
VES 6, 8, 10/12 mg cohort x 10 doses

CD4, Plasma HIV-1 RNA
HIV DNA ELISpot*, flow*
ISG, cytokines, cell activation
VES PK

*Measurement of HIV specific T-cell responses
## Baseline Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PBO n=12</th>
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<th>8 mg n=6</th>
<th>10/12 mg n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>47 (26-62)</td>
<td>46 (28-58)</td>
<td>45 (27-58)</td>
<td>54 (43-57)</td>
<td>45 (28-55)</td>
<td>45 (31-60)</td>
<td>53 (23-66)</td>
</tr>
<tr>
<td>Male, n</td>
<td>12</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Median CD4, cells/mm³</td>
<td>624</td>
<td>875</td>
<td>658</td>
<td>504</td>
<td>757</td>
<td>676</td>
<td>814</td>
</tr>
<tr>
<td>Median time from Dx to ART, y</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Median total time on ART, y</td>
<td>10</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Median Pre-ART VL (log10 copies/mL)</td>
<td>5.34</td>
<td>4.35</td>
<td>4.64</td>
<td>4.48</td>
<td>5.17</td>
<td>3.48</td>
<td>4.01</td>
</tr>
</tbody>
</table>

*Dx, diagnosis.*
Laboratory Abnormalities

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<tr>
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<th>4 mg n=6</th>
<th>6 mg n=6</th>
<th>8 mg n=6</th>
<th>10/12 mg n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>7 (58)</td>
<td>5 (83)</td>
<td>5 (83)</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (17)</td>
<td>1 (17)</td>
<td>0</td>
<td>1 (17)</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (17)a</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (17)b</td>
</tr>
</tbody>
</table>

Participants were counted once for the maximum severity for each laboratory test.

- Participant with hematuria with confirmed menses;  
- Participants with elevated creatinine kinase due to strenuous exercise

- No dose dependent trends in lab abnormalities
Pharmacokinetics

- VES was rapidly absorbed ($T_{\text{max}}$ 1-4 hours)
- Exposure was generally dose proportional

*Below limit of quantification at 48 hours*