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

Goal: Combine TLR7 agonist, bNAb, therapeutic vaccine

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


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

**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

**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

NCT02858401
PLWH: People Living with HIV; ISG, interferon-stimulated gene; PBO, placebo; PD, pharmacodynamics; PK, pharmacokinetics; VES, vesatolimod.
Vesatolimod Dose Escalation: Design and Assessments

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

<table>
<thead>
<tr>
<th></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><strong>Median age, y</strong>&lt;br&gt;(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><strong>Male, n</strong></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><strong>Median CD4, cells/mm³</strong></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><strong>Median time from Dx to ART, y</strong></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><strong>Median total time on ART, y</strong></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><strong>Median Pre-ART VL</strong>&lt;br&gt;(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.
Safety
Overall Safety

<table>
<thead>
<tr>
<th>Participants, n (%)</th>
<th>PBO n=12</th>
<th>1 mg n=6</th>
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<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>

- 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
## 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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</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>Myalgia</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>
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URI: upper respiratory tract infection
Laboratory Abnormalities

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<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)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (17)</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
Pharmacokinetics

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

Exposure was generally dose proportional

*Below limit of quantification at 48 hours
Pharmacodynamics
NK Cell Activation

Similar trends observed in CD4 and CD8 T lymphocytes

1st administration at each dose level shown
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

Participants, n=36

Dose

10/12 mg

8 mg

6 mg

4 mg

2 mg

1 mg

Placebo

White cells are missing data

ISG, Interferon-stimulated gene
Virologic Assessments
Virologic Results

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<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>
<td>3</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>
<td>24–27</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.

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