Introduction

• Vesatolimod (VES; formerly known as GS-9620) is an orally administered investigational toll-like receptor-7 (TLR7) agonist in clinical development for the cure of HIV-1 infection; nonclinical and clinical studies have established preliminary safety and efficacy of VES alone or in combination with other agents 

• Stimulation of TLR7 results in activation of interferon regulatory factor-7 and nuclear factor-kB signaling, which induces the production of type 1 interferons (IFNs) and other inflammatory cytokines, ultimately leading to stimulation of innate and adaptive immune responses 

• Type 1 IFN responses can elicit a complex cascade of events in response to viral infections and influenza-like adverse events (flu-like AEs); common side effects associated with type 1 IFN therapy 

• VES selectively activates TLR7 and induces IFN-stimulated gene expression, resulting in increased circulating cytokines and chemokines, and activation of immune response cells 

• VES may be associated with flu-like AEs; a broader understanding of the relationship between flu-like AEs and the VES mechanism of action (MOA) is needed to support future combination studies 

Objective

• To investigate VES pharmacokinetics (PK), pharmacodynamic (PD) responses, and biomarkers of inflammation to understand the MOA underlying flu-like AEs

Methods

Summary of 8 Studies Included in the Pooled Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Treatment</th>
<th>Drug Administered</th>
<th>Drug Doses</th>
<th>Dose Range (mg)</th>
<th>Study Outcome</th>
<th>Study Length</th>
<th>Participants</th>
<th>Participants</th>
<th>Start/End Date</th>
<th>Enrollment</th>
<th>Follow-Up</th>
<th>Key Investigators</th>
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</thead>
<tbody>
<tr>
<td>NCT02579382</td>
<td>Multicenter</td>
<td>Placebo-controlled, multicenter study</td>
<td>1, 2, 4 VES</td>
<td>0.3, 1, 2, 4</td>
<td>156</td>
<td>Flu-Like AEs</td>
<td>12 wks</td>
<td>192 (164/28)</td>
<td>2015-2017</td>
<td>204</td>
<td>12 wks</td>
<td>Prague, Czech Rep.</td>
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<tr>
<td>NCT01590654</td>
<td>Multicenter</td>
<td>Placebo-controlled, single- and 2-dose study</td>
<td>0.3, 1, 2, 4 VES</td>
<td>0.3, 1, 2, 4</td>
<td>51</td>
<td>Flu-Like AEs</td>
<td>1 wk</td>
<td>51 (43/8)</td>
<td>2014-2015</td>
<td>12 wks</td>
<td>12 wks</td>
<td>Warsaw, Poland</td>
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<tr>
<td>NCT02579383</td>
<td>Multicenter</td>
<td>Placebo-controlled, 4-dose study</td>
<td>0.3, 1, 2, 4 VES</td>
<td>0.3, 1, 2, 4</td>
<td>36</td>
<td>Flu-Like AEs</td>
<td>1 wk</td>
<td>36 (31/5)</td>
<td>2015-2016</td>
<td>8 wks</td>
<td>8 wks</td>
<td>San Francisco, CA</td>
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<tr>
<td>NCT03195604</td>
<td>Multicenter</td>
<td>Placebo-controlled, 5-dose study</td>
<td>0.3, 1, 2, 4 VES</td>
<td>0.3, 1, 2, 4</td>
<td>24</td>
<td>Flu-Like AEs</td>
<td>1 wk</td>
<td>24 (22/2)</td>
<td>2016-2017</td>
<td>12 wks</td>
<td>12 wks</td>
<td>San Francisco, CA</td>
<td></td>
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<tr>
<td>NCT02914960</td>
<td>Single-center</td>
<td>Placebo-controlled, single-dose study</td>
<td>1, 2, 4 VES</td>
<td>1, 2, 4 VES</td>
<td>24</td>
<td>Flu-Like AEs</td>
<td>1 wk</td>
<td>24 (22/2)</td>
<td>2016-2017</td>
<td>8 wks</td>
<td>8 wks</td>
<td>San Francisco, CA</td>
<td></td>
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<tr>
<td>NCT03271641</td>
<td>Multicenter</td>
<td>Placebo-controlled, adaptive study</td>
<td>0.3, 1, 2, 4 VES</td>
<td>0.3, 1, 2, 4</td>
<td>126</td>
<td>Flu-Like AEs</td>
<td>1 wk</td>
<td>126 (95/31)</td>
<td>2016-2017</td>
<td>12 wks</td>
<td>12 wks</td>
<td>Pittsburgh, PA</td>
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<tr>
<td>NCT02579382</td>
<td>Multicenter</td>
<td>Placebo-controlled, adaptive study</td>
<td>0.3, 1, 2, 4 VES</td>
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<td>126</td>
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<td>12 wks</td>
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<td>Pittsburgh, PA</td>
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</tbody>
</table>

AE analysis strategy

• Flu-like AE data were pooled from 8 clinical studies in HIV, people with chronic HBV, and people with HIV

• A subset of flu-like AEs, selected based on clinical significance and termed flu-like AEs of interest (AEIs), was also analyzed

VES PK analysis

• Plasma VES concentration was assessed in all or a subset of participants across the 8 studies using high-performance liquid chromatography–tandem mass spectroscopy

• Maximal concentration (Cmax) and area under the concentration-time curve to infinity after a single dose (AUC0-∞) were estimated by standard noncompartmental methods using Phoenix WinNonlin® 7.0 software (Certara, Princeton, New Jersey, US)

Biomarker assay and analysis strategy

• VES PD response was assessed through measuring several serum cytokines (INF-γ-induced protein 10 [IP-10], interleukin-1 receptor antagonist [IL-1RA], IFN-inducible T-cell alpha chemotactant [ITAC]), and IFNα; markers of inflammation included INFα, tumor necrosis factor-α (TNFα), IL-6, and C-reactive protein (CRP)

• Assay platform included high-sensitivity Ciraplex ULTRA, Ultrasensitive Assay (Aushon Biosystems, Inc., Billerica, Massachusetts, USA) and Ultrasensitive Immunoassay (Rules Based Medicine, Austin, Texas, USA) for IFNα and IL-1RA, as well as enzyme-linked immunosorbent assay for CRP at the University of Pittsburgh; further, whole blood cell immunophenotyping was analyzed using flow cytometry to evaluate the frequency of activated natural killer (NK) cells (CD56+ NK; LabCorp Drug Development, Indianapolis, Indiana, USA)

• Fold change from baseline for each biomarker analytic was calculated prior to consolidating the data from the 8 studies for further analysis

Statistical analysis

• Wilcoxon rank-sum test was used to compare differences in the data obtained between groups, whereas chi-square test was used to analyze associations between early and later flu-like AEs (the publication analysis is instead as described in each figure legend)

Flu-Like AEs and AEIs

<table>
<thead>
<tr>
<th>AE/Grade</th>
<th>%</th>
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<th>%</th>
<th>AE/Grade</th>
<th>%</th>
<th>AE/Grade</th>
<th>%</th>
<th>AE/Grade</th>
<th>%</th>
<th>AE/Grade</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>100</td>
<td>Chills</td>
<td>100</td>
<td>Headache</td>
<td>100</td>
<td>Malaise</td>
<td>100</td>
<td>Flu-like illness</td>
<td>100</td>
<td>Fever</td>
<td>100</td>
</tr>
</tbody>
</table>

Flu-like AEs Were Mostly Mild Across All 8 Studies

The most common flu-like AEs were pyrexia, chills, and headache

Frequency and Subtype of Flu-Like AEIs in All 8 Studies

VES Increased PD Biomarkers 24 Hours After 1st VES Administration in Dose-Dependent Manner

Higher Increases in PD Biomarkers, IL-6, and CD69 NK in Participants With Flu-Like AEIs 24 Hours After 1st Dose

Significant Association of Early and Later Flu-Like AEIs

Conclusions

• In this pooled analysis of 8 clinical studies, VES was generally safe and well tolerated

• Flu-like AEs were more common with VES vs placebo; the most common flu-like AEs were pyrexia, chills, and headache

• The data suggest a link between flu-like AEIs and VES MOA:
  - Flu-like AE frequency increased with VES dose and exposure, and was highest after doses 1 and 2
  - Dose-dependent elevation of PD biomarkers (IFNα, IL-1RA, IP-10, and ITAC) was observed
  - Some inflammatory and PD biomarkers were higher at 24 hours in participants with vs without flu-like AEIs (IL-6, CD69 NK, IFNα, IL-1RA, and IP-10)
  - There were no dose-dependent changes in inflammatory biomarkers (CRP, IFNγ, IL-6, and TNFα)
  - Early occurrence of flu-like AEIs (after doses 1–3) was predictive of occurrence after later doses, supporting adaptive clinical monitoring

• The relationship between VES PD and efficacy in the setting of HIV remission strategies will be explored in future studies

Presented at HIV Glasgow 2022, 23-26 Oct, Glasgow, UK

A Pooled Analysis of 8 Clinical Studies Suggests a Link Between Influenza-Like Adverse Events and Pharmacodynamics of the Toll-Like Receptor-7 Agonist Vesatolimod

Sharon Riddler, Yanhui Cal, Yanan Zheng, Liao Zhang, Donovan Verrill, Xiaopeng Liu, Daina Lim, Elena Vendrame, Devi SenGupta

1 University of Pittsburgh, Pennsylvania, US; 2 Gilead Sciences, Inc., Foster City, California, US