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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

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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[1-4]
- Stimulation of TLR7 results in activation of interferon regulatory factor-7 and nuclear factor k-B 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[4] and influenza-like adverse events (flu-like AEs) are common side effects associated with type 1 IFN therapy[5,6]
- VES selectively activates TLR7 and induces IFN-stimulated gene expression, resulting in increased circulating cytokines and chemokines, and activation of immune response cells[7-10]
- 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

Study/ ClinicalTrials.gov ID	Population	Design	Total Participants (VES/Placebo)	VES Administration	VES Dose, mg	End Points
GS-US-243-0101/ NA	Healthy subjects	Phase 1, randomized, double-blind, placebo-controlled study	75 (55/20)	Single oral dose	0.3, 1, 2, 4, 6, 8, 12	Safety, tolerability, PK, and PD of VES
GS-US-283-0102/ NCT01590654	Virologically suppressed chronic HBV	Phase 1, double-blind, randomized, placebo-controlled, single- and multiple-dose–ranging, adaptive study	51 (43/8)	Single dose or 2 doses 1 wk apart	0.3, 1, 2, 4	Safety, tolerability, PK, PD, and antiviral activity of VES
GS-US-283-0106/ NCT01590641	Treatment-naive chronic HBV	Phase 1, double-blind, randomized, placebo-controlled, single- and multiple-dose–ranging, adaptive study	49 (41/8)	Single dose or 2 doses 1 wk apart	0.3, 1, 2, 4	
GS-US-283-1059/ NCT02166047	Virologically suppressed chronic HBV	Phase 1, double-blind, randomized, placebo-controlled, multiple-dose–ranging, adaptive study	162 (146/16)	Weekly dose for 12 wk	1, 2, 4	
GS-US-283-1062/ NCT02579382	Chronic HBV not on treatment	Phase 2, randomized, double-blind, placebo-controlled, multicenter study	192 (164/28)	Weekly dose for 12 wk	1, 2, 4	Safety and efficacy of VES in combination with TDF
GS-US-382-1450/ NCT02858401	Virologically suppressed HIV-1	Phase 1b, randomized, blinded, placebo-controlled, dose-escalation study	48 (36/12)	Biweekly dose for 10 wk	1, 2, 4, 6, 8, 10, 12	Safety and biological activity of VES
GS-US-382-3961/ NCT03060447	ARV-treated controllers with HIV-1	Phase 1b, randomized, double-blind, placebo-controlled study	25 (17/8)	Biweekly dose for 10 wk	4, 6, 8	Safety and efficacy of VES
GS-US-420-5372/ NA	Healthy subjects	Phase 1, randomized, placebo-controlled, staggered, multiple-ascending–dose study	4 (3/1)	Single dose	8	Safety, tolerability, and PK of EVM in combination with VES

ARV = antiretroviral; EVM = elipovimab (formerly known as GS-9722); HBV = hepatitis B virus; TDF = tenofovir disoproxil fumarate.

- AE analysis strategy
  - Flu-like AE data were pooled from 8 clinical studies in HV, 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 (C_{max}) and area under the concentration-time curve to infinity after a single dose (AUC_{inf}) 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 (IFNγ-induced protein 10 [IP-10], interleukin (IL)-1 receptor antagonist [IL-1RA], IFN-inducible T-cell-α chemoattractant [ITAC], and IFNα); markers of inflammation included IFNγ, 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, US) and Ultrasensitive Immunoassay (Rules Based Medicine, Austin, Texas, US) 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 ($CD69^+$ NK; Labcorp Drug Development, Indianapolis, Indiana, US)
  - Fold change from baseline for each biomarker analyte 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 AEIs (the specific statistical analysis method is described in each figure legend)

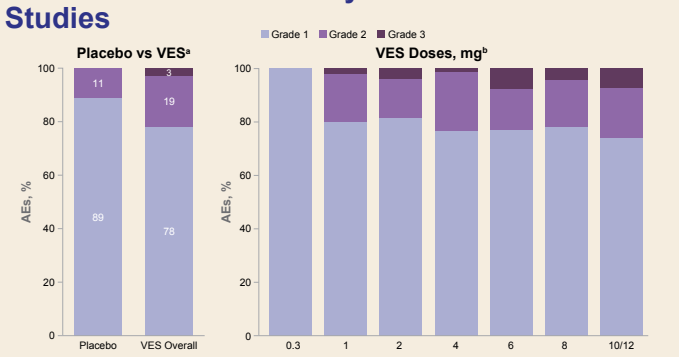
Flu-Like AEs and AEIs

Flu-Like AE (All Grades)	Flu-Like AEI
Cytokine release syndrome	Cytokine release syndrome, any grade
Hemophagocytic lymphohistiocytosis	
Cytokine storm	
Capillary leak syndrome	
Pyrexia	Pyrexia, any grade
Chills	Chills, any grade
Headache	Headache, Grade ≥ 2
Fatigue	Fatigue, Grade ≥ 2
Cancer fatigue	
Nausea	
Vomiting	
Systemic inflammatory response syndrome	
Hypotension	
Hypoxia	
Flu-like illness	Flu-like illness, any grade
Myalgia	Myalgia, Grade ≥ 2
Influenza	Influenza, any Grade
Malaise	Malaise, Grade ≥ 2

Preferred/lowest-level terms from Medical Dictionary for Regulatory Activities.

Results

Flu-Like AEs Were Mostly Mild Across All 8 Studies

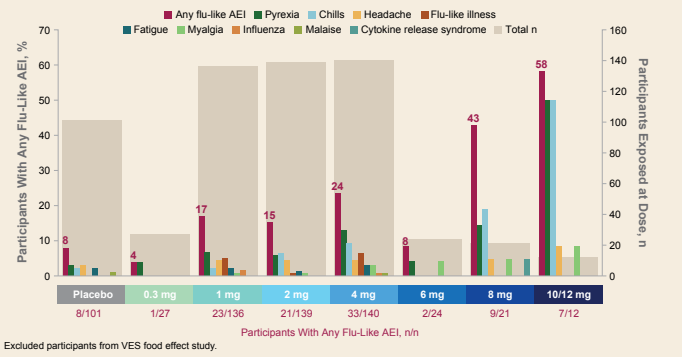


AEs with missing grades were not included in analysis; based on highest grade/dose in event of multiple grades/doses. [a]Included fed/fasted/empty stomach; [b]Excluded participants from VES food effect study.

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

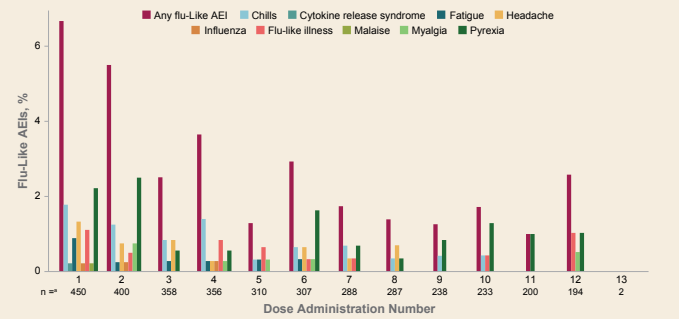
- The most common flu-like AEIs were pyrexia, chills, and headache

Frequency of Flu-Like AEIs Increased by VES Dose Level



Excluded participants from VES food effect study.

Most Flu-Like AEIs Occurred at 1st and 2nd Doses



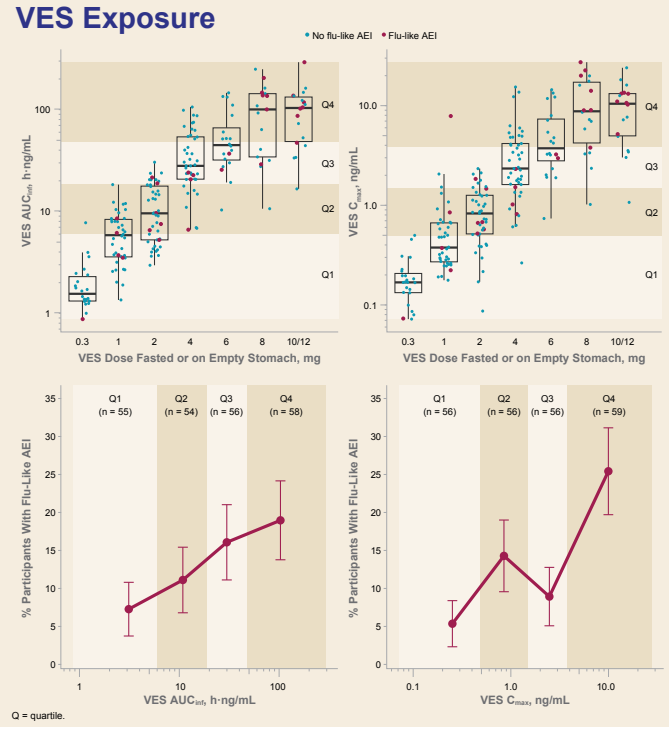
[a]Number of participants who received the number of VES administrations indicated in *x axis*; analysis excludes participants who received only single dose of VES.

Significant Association of Early and Later Flu-Like AEIs

Participants With Any Flu-Like AEI, n/n (%)	No Later Flu-Like AEI	Later Flu-Like AEI
After Dose 1	14/311 (5)	12/52 (23)
	$P < 0.001$	
After Dose 2	14/308 (5)	8/52 (15)
	$P = 0.003$	
After Dose 3	6/306 (2)	7/52 (14)
	$P < 0.001$	

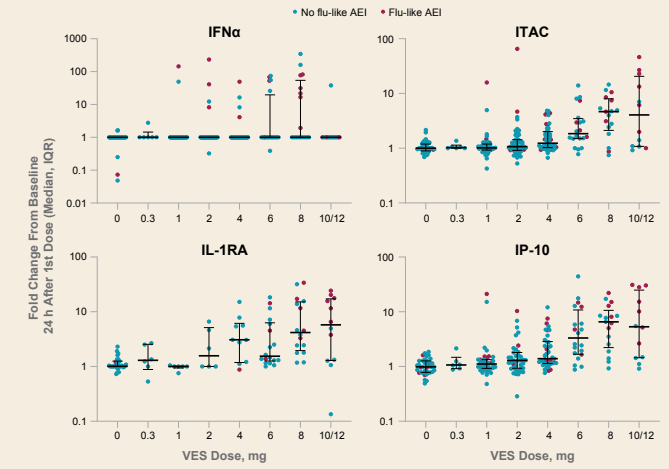
Later doses defined as Doses 4-13; nominal *P* values generated from chi-square test.

Incidence Rate of Flu-Like AEIs Increased With VES Exposure



Q = quartile.

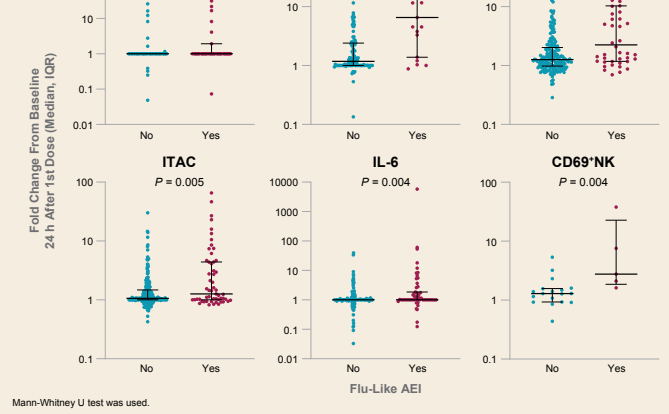
VES Increased PD Biomarkers 24 Hours After 1st VES Administration in Dose-Dependent Manner



Excluded participants from VES food effect study. IQR = interquartile range.

- No significant dose-dependent changes in inflammation markers IFNγ, TNFα, IL-6, and CRP between participants with and without flu-like AEIs 24 hours after VES dose

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



Mann-Whitney U test was used.

Conclusions

- In this pooled analysis of 8 clinical studies, VES was generally safe and well tolerated
- Flu-like AEIs were more common with VES vs placebo; the most common flu-like AEIs were pyrexia, chills, and headache
- The data suggest a link between flu-like AEIs and VES MOA:
  - Flu-like AEI 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

References: **1.** Bekeredjian-Ding IB, et al. *J Immunol.* 2005;174:4043-50; **2.** Bender AT, et al. *ImmunoHorizons.* 2020;4:93-107; **3.** Kawai T, Akira S. *Nat Immunol.* 2010;11:373-84; **4.** Kawai T, Akira S. *Trends Mol Med.* 2007;13:460-9; **5.** Ng CT, et al. *Cell.* 2016;164:349-52; **6.** Sleijfer S, et al. *Pharm World Sci.* 2005;27:423-31; **7.** Fosdick A, et al. *J Pharmacol Exp Ther.* 2014;348:96-105; **8.** Lawitz EJ, et al. *Antivir Ther.* 2015;20:699-708; **9.** Niu C, et al. *J Hepatol.* 2018;68:922-31; **10.** Roethle PA, et al. *J Med Chem.* 2013;56:7324-33. **Acknowledgments:** We extend our thanks to the participants, their partners, and families. Special thanks to the study teams. *Clinical Investigators:* Sharon Riddler, Steven Deeks, Moti Ramgopal, Cynthia Brinson, Edwin DeJesus, Anthony Mills, Peter Shalit; *Safety, PK, and Biomarker Analysis:* Norman Jone, Valerie Girling (UCSF–Core Immunology Lab, San Francisco, California, US); Yanhui Cai, Yanan Zheng, Liao Zhang, Donovan Verrill, Xiaopeng Liu, Daina Lim, Christiaan R. de Vries, Elena Vendrame, Devi SenGupta, Jeffrey J. Wallin (Gilead). These 8 clinical studies and analyses were funded by Gilead. Editing and production assistance were provided by Clint Earnheart of BioScience Communications, New York, New York, US, funded by Gilead.

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