

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 agents¹⁻⁴
- Stimulation of TLR7 results in activation of interferon regulatory factor-7 and nuclear factor κ-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 infections⁴ 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 cells⁷⁻¹⁰
- 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-243-01011 NA	Healthy subjects	Phase 1, randomized, double-blind, placebo-controlled study	75 (55/20)	Single oral dose	0.3, 1, 2, 4, 8, 12	Safety, tolerability, PK, and PD of VES
GS-US-283-01022 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-283-01067 NCT01590641	Treatment-naïve 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	Safety, tolerability, PK, PD, and antiviral activity of VES
GS-US-283-10599 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	Safety and efficacy of VES in combination with TDF
GS-US-283-10822 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 NCT02859401	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-382-38611 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-420-03722 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 = elivovimab (formerly known as GS-9722); HBV = hepatitis B virus; NA = not applicable; 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, 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 AEs (the specific statistical analysis method is described in each figure legend)

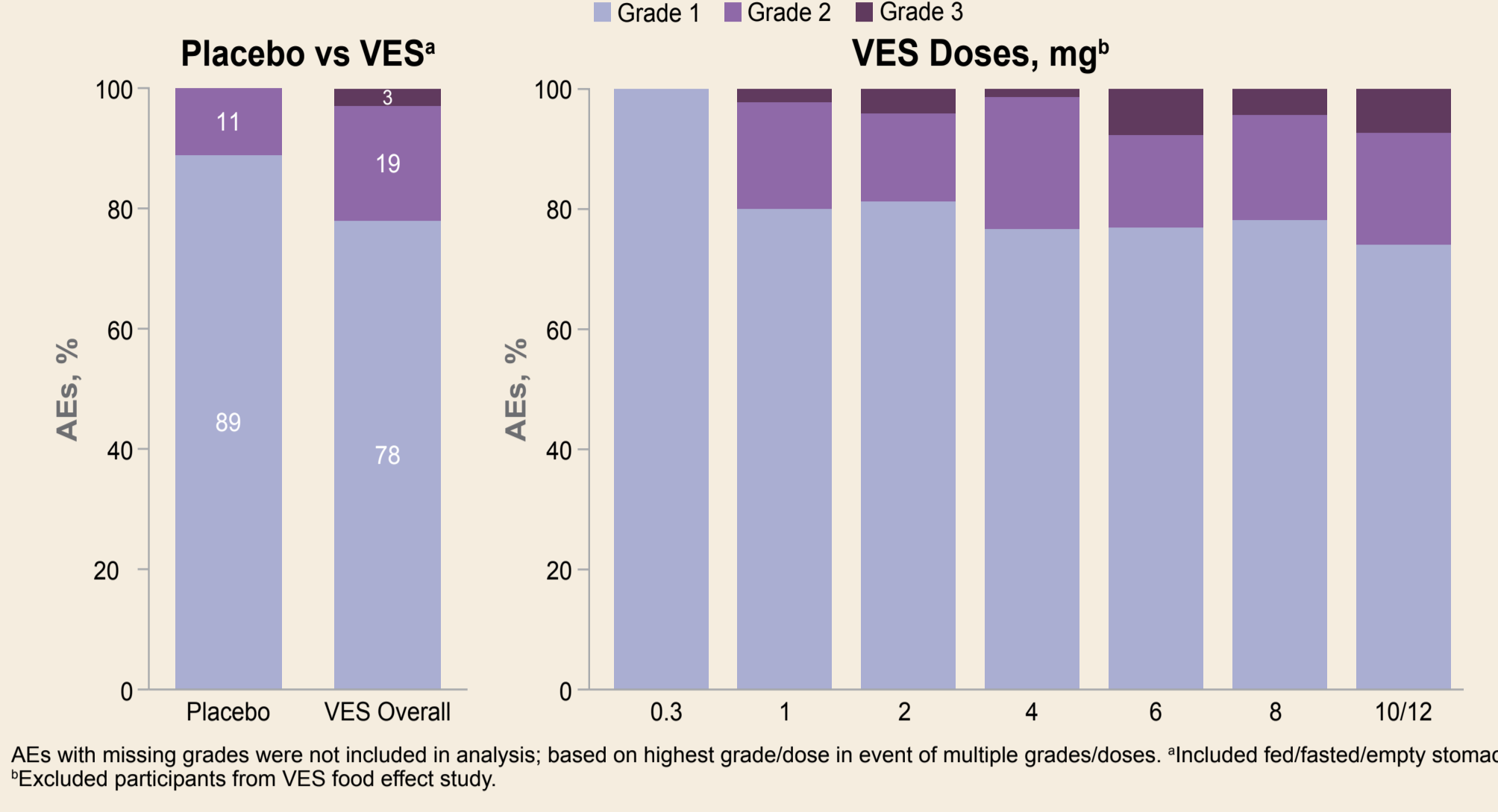
Flu-Like AEs and AEs

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

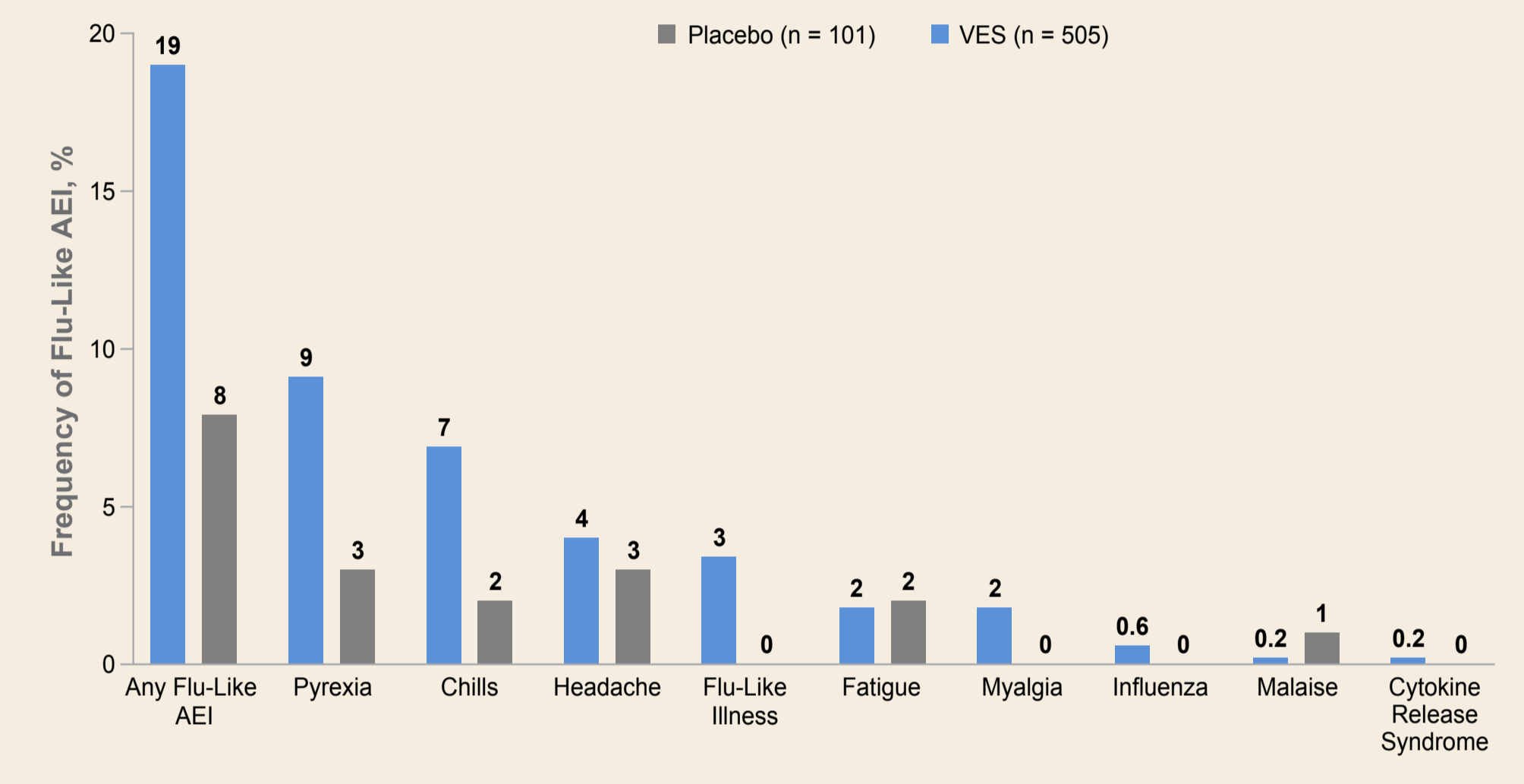
Preferred/lowest-level terms from Medical Dictionary for Regulatory Activities. AEIs = AEs of interest.

Results

Flu-Like AEs Were Mostly Mild Across All 8 Studies

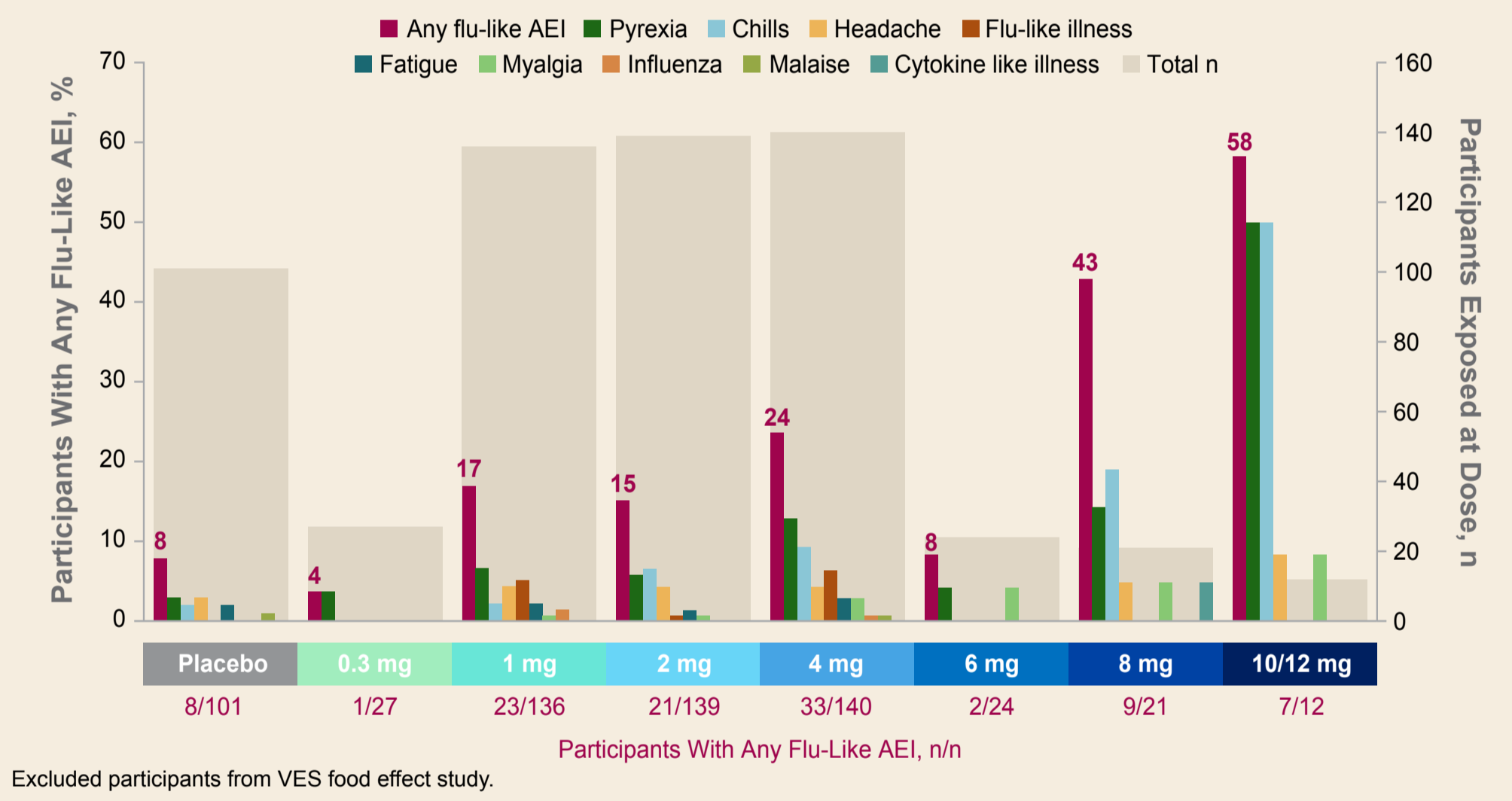


Frequency and Subtype of Flu-Like AEs in All 8 Studies

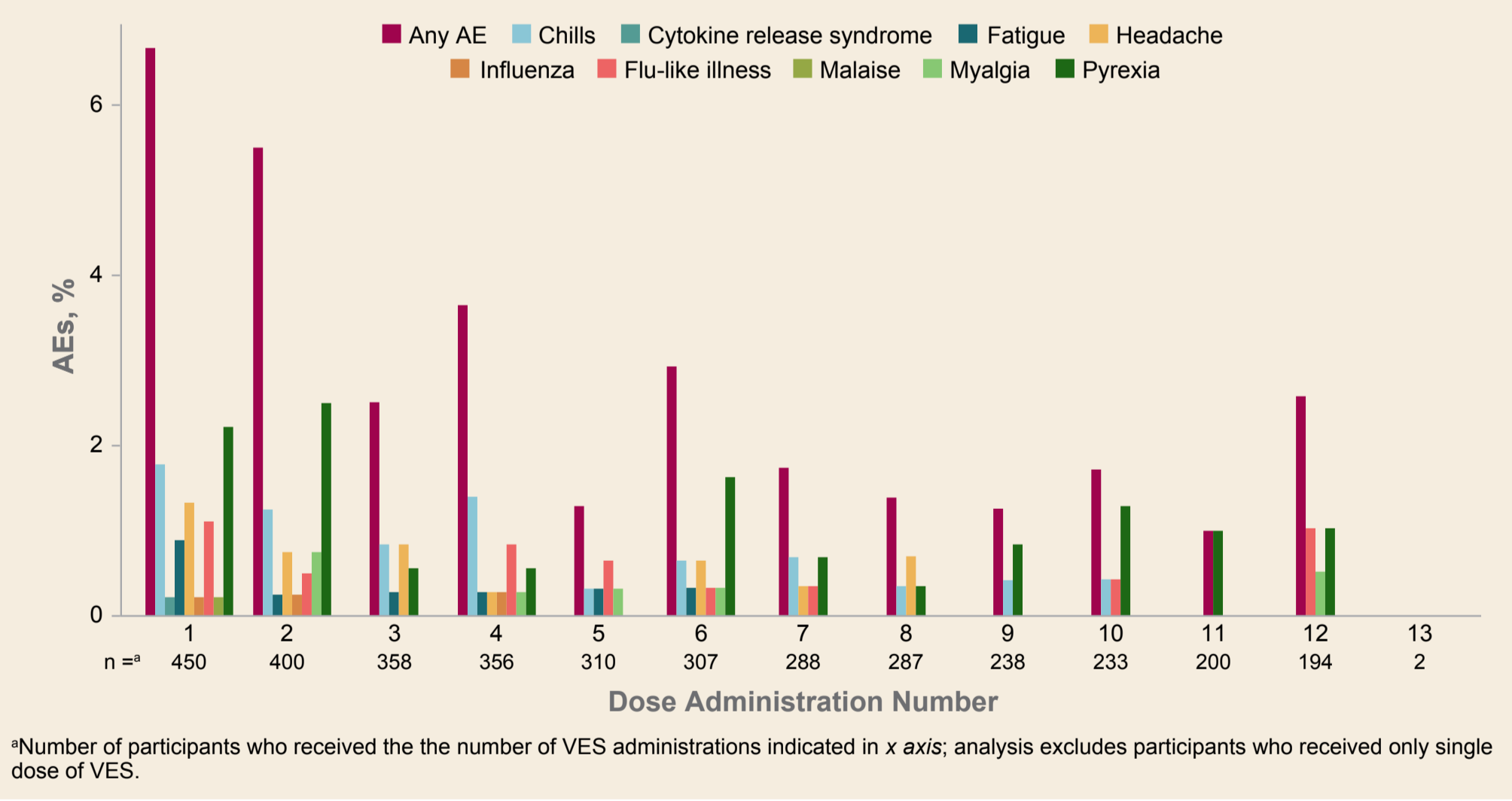


- The most common flu-like AEs were pyrexia, chills, and headache

Frequency of Flu-Like AEs Increased by VES Dose Level



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



Significant Association of Early and Later Flu-Like AEs

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)
After Dose 2	14/308 (5)	8/52 (15)
After Dose 3	6/306 (2)	7/52 (14)

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

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 AEs 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 AEs (IL-6, CD69⁺ NK, IFNα, IL-1RA, and IP-10)
- There were no dose-dependent changes in inflammatory biomarkers (CRP, IFNγ, IL-6, TNFα)
- Early occurrence of flu-like AEs (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. Bekerejian-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. Szeifler S, et al. *Pharm World Sci*. 2005;27:423-31. 7. Fiedick 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. Roethlis 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, Moli Ramgopal, Cynthia Brinson, Edson Delvescu, Anthony Mills, Peter Shull, Safety, PK, and Biomarker Analysis: Norman Jones, Valerie Gitting (UCSF–Core Immunology Lab, San Francisco, California, US); Yanhui Cai, Yanan Zheng, Liao Zhang, Donovan Verrill, Xiaopeng Liu, Daina Lim, Christian R. de Vries, Elena Vendrame, Devi SenGupta, Jeffrey J. Wallin (Gilead). These 8 clinical studies and analysis were funded by Gilead. Editing and production assistance were provided by Carl Eimheart of Bioscience Communications, New York, New York, US, funded by Gilead.