

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

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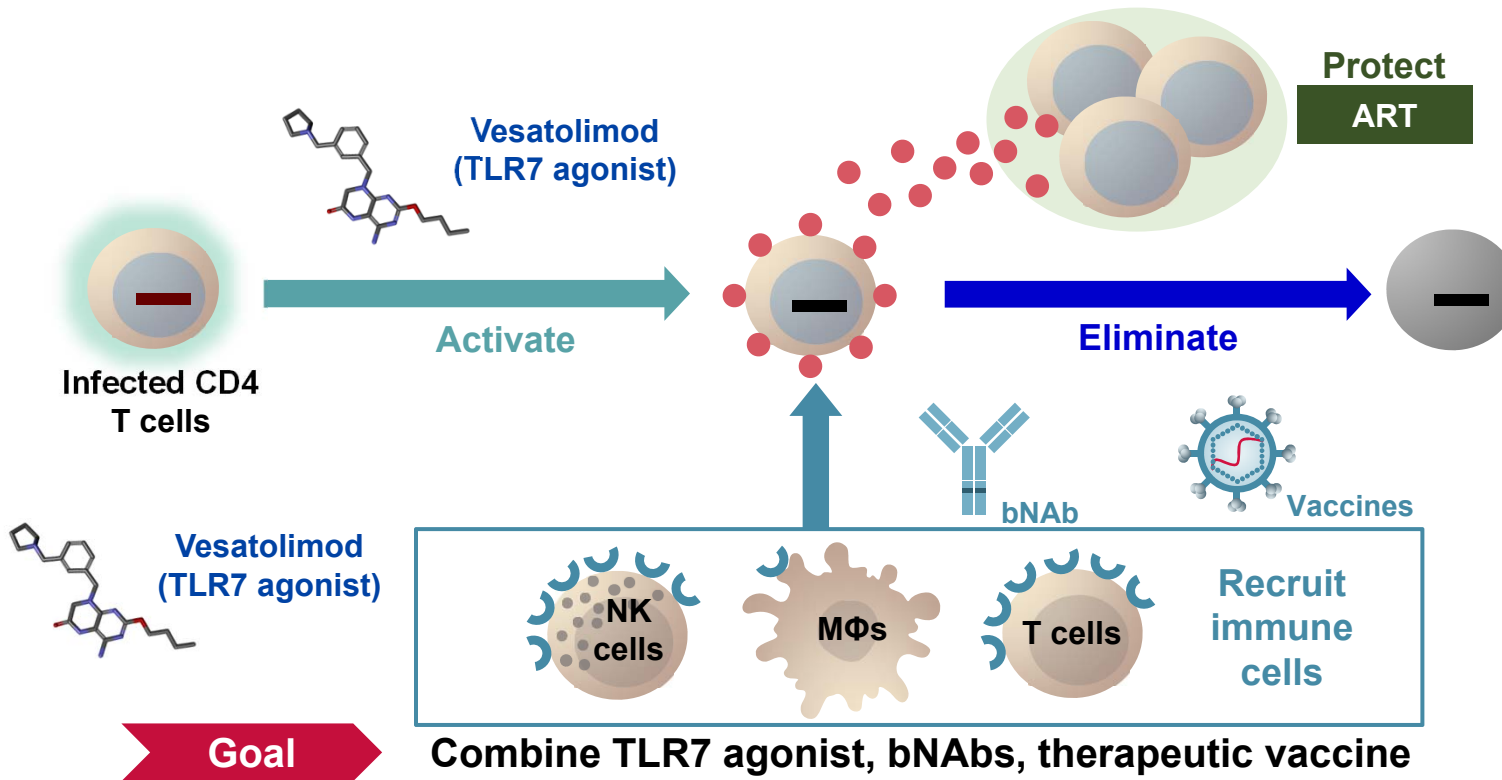
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Disclosures

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Immune-Based Strategies to Eliminate HIV Reservoirs

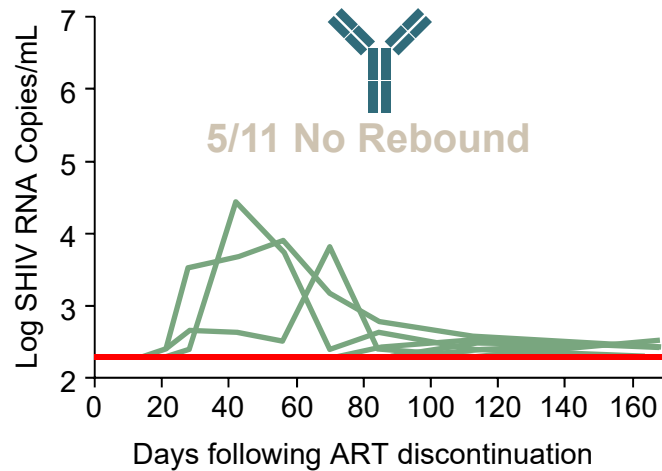


ART, antiretroviral therapy; bNAb, broadly neutralizing antibody; MΦs, macrophages; NK, natural killer; TLR7, toll-like receptor-7.

Proof of Concept in Nonhuman Primate Model

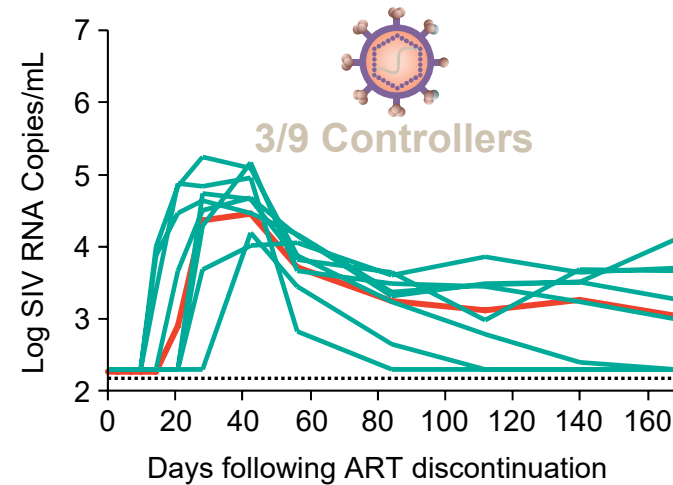


TLR7 + bNAb



Modified from Borducchi E, et al. Nature 2018;563:360-4.

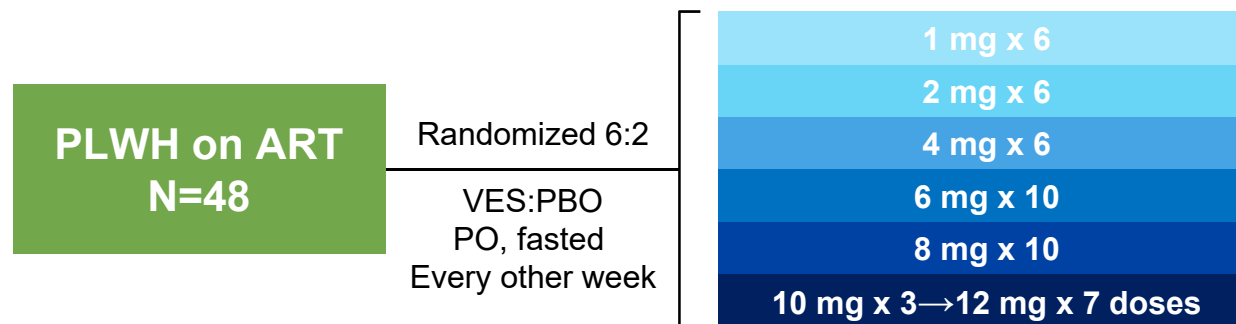
TLR7 + Vaccine



Modified from Borducchi E, et al. Nature 2016;540:284-7.

SHIV, simian/human immunodeficiency virus; SIV, simian immunodeficiency virus.

Vesatolimod Dose Escalation Study in PLWH



Key inclusion criteria:

- ◆ CD4 count ≥ 400 cells/ μ L
- ◆ HIV-1 RNA levels < 50 copies/mL x ≥ 1 year
- ◆ Pre-ART CD4 nadir ≥ 200 cells/ μ L

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.

Overall Safety

Participants, n (%)	PBO n=12	1 mg n=6	2 mg n=6	4 mg n=6	6 mg n=6	8 mg n=6	10/12 mg n=6
Any grade AE	9 (75)	4 (67)	4 (67)	2 (33)	4 (67)	5 (83)	4 (67)
Grade 2	2 (17)	3 (50)	2 (33)	1 (17)	1 (17)	2 (33)	1 (17)
Study drug- related AE	2 (17)	0	1 (17)	1 (17)	1 (17)	3 (50)	3 (50)

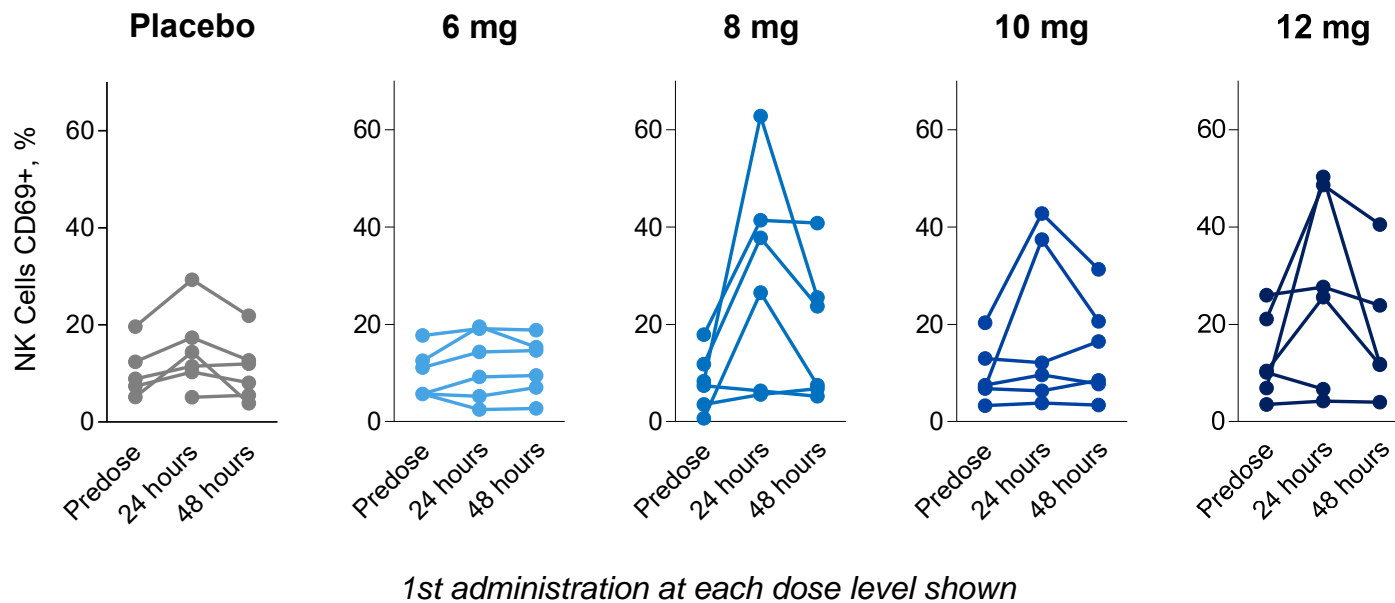
- ◆ 1 Grade 3 AE (abdominal pain) and 1 serious AE (diverticulitis; 2 mg cohort)
 - Both unrelated to study drug and occurring in same participant
- ◆ No discontinuations due to AEs; no Grade 4 AEs; no deaths

Common Adverse Events (> 1 participant by cohort)

Participants, n (%)	PBO n=12	1 mg n=6	2 mg n=6	4 mg n=6	6 mg n=6	8 mg n=6	10/12 mg n=6
Any AE	9 (75)	4 (67)	4 (67)	2 (33)	4 (67)	5 (83)	4 (67)
Cough	3 (25)	1 (17)	0	1 (17)	1 (17)	0	0
Headache	2 (17)	1 (17)	1 (17)	0	0	1 (17)	1 (17)
Fatigue	3 (25)	2 (33)	0	1 (17)	1 (17)	0	3 (50)
Nausea	1 (8)	2 (33)	1 (17)	0	0	1 (17)	1 (17)
Myalgia	1 (8)	0	0	0	2 (33)	1 (17)	1 (17)
Sinus Congestion	1 (8)	2 (33)	1 (17)	0	1 (17)	0	0
URI	0	0	0	0	0	2 (33)	0

URI: upper respiratory tract infection

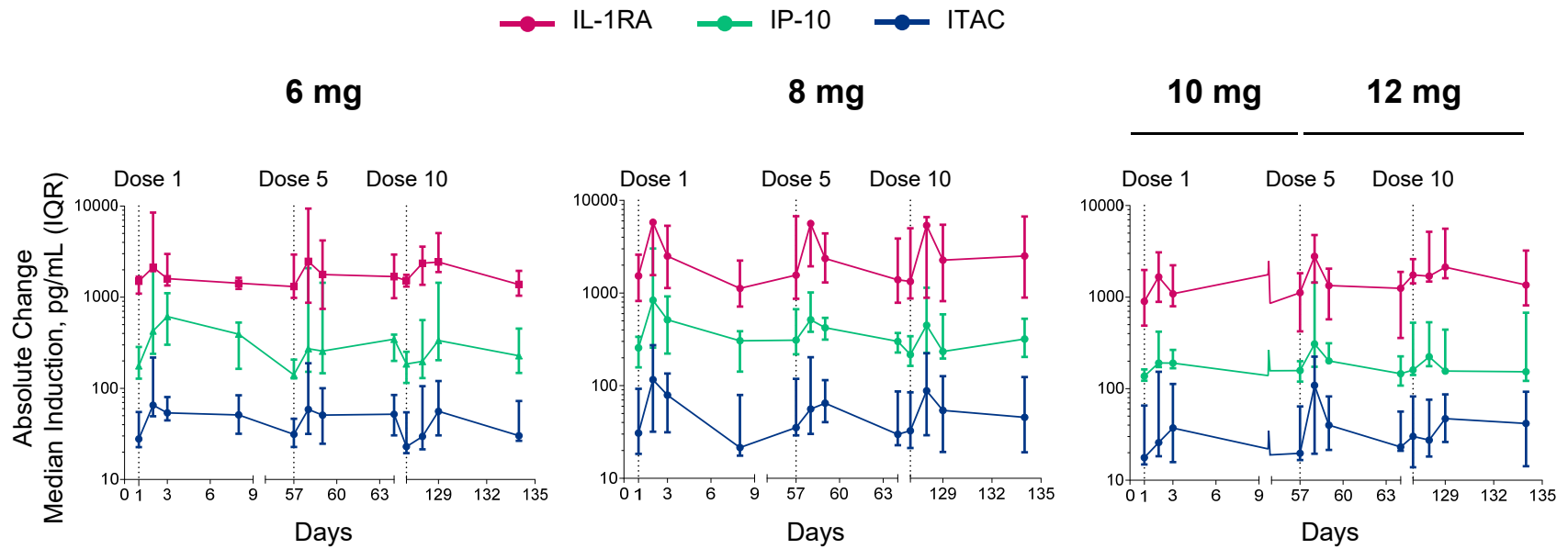
NK Cell Activation



1st administration at each dose level shown

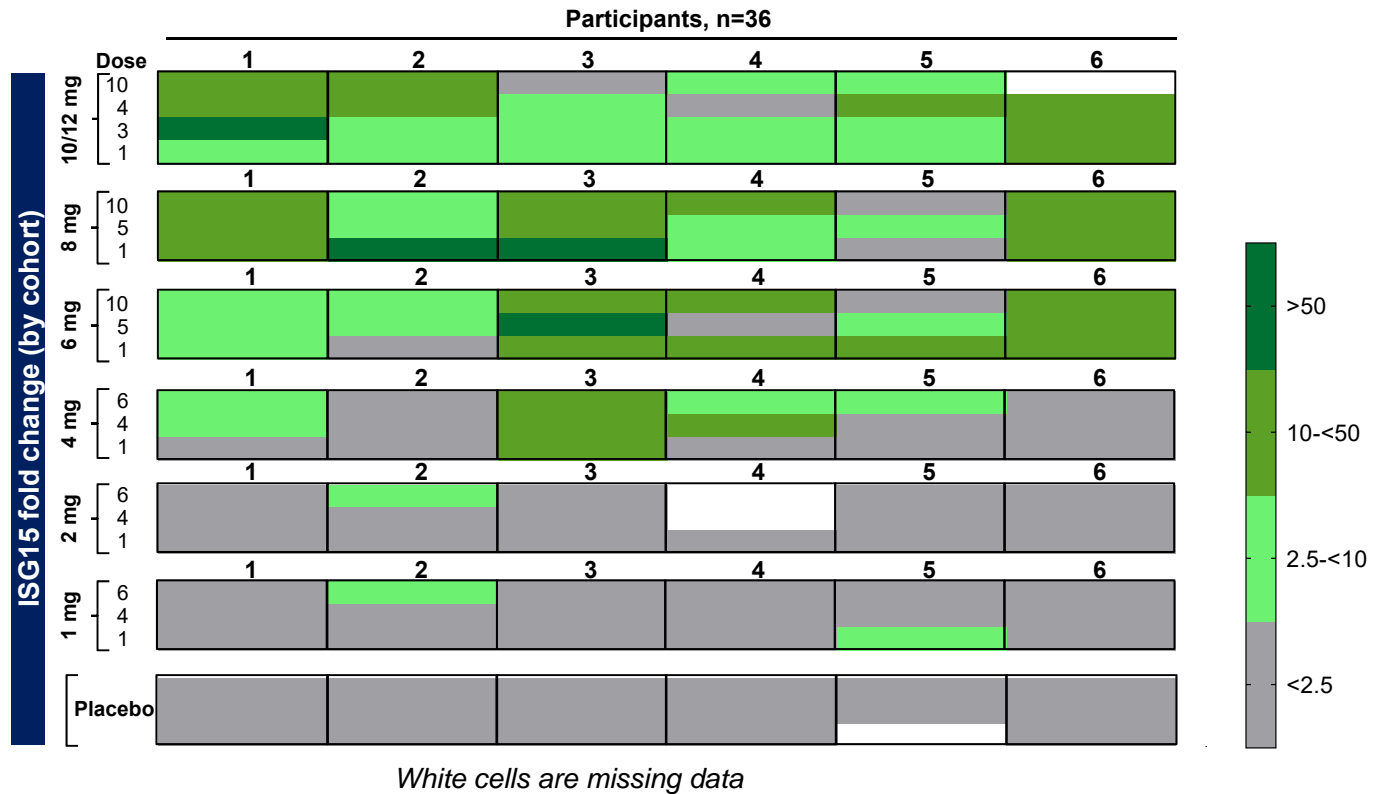
- ◆ Similar trends observed in CD4 and CD8 T lymphocytes

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



ISG, Interferon-stimulated gene

Virologic Results

	PBO n=12	1 mg n=6	2 mg n=6	4 mg n=6	6 mg n=6	8 mg n=6	10/12 mg n=6
Any pVL > 20 copies/mL, n	8	2	1	2	1	0	3
pVL range, copies/mL	21-2430	21-42	21	23-69	32	-	24-27

- ◆ 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

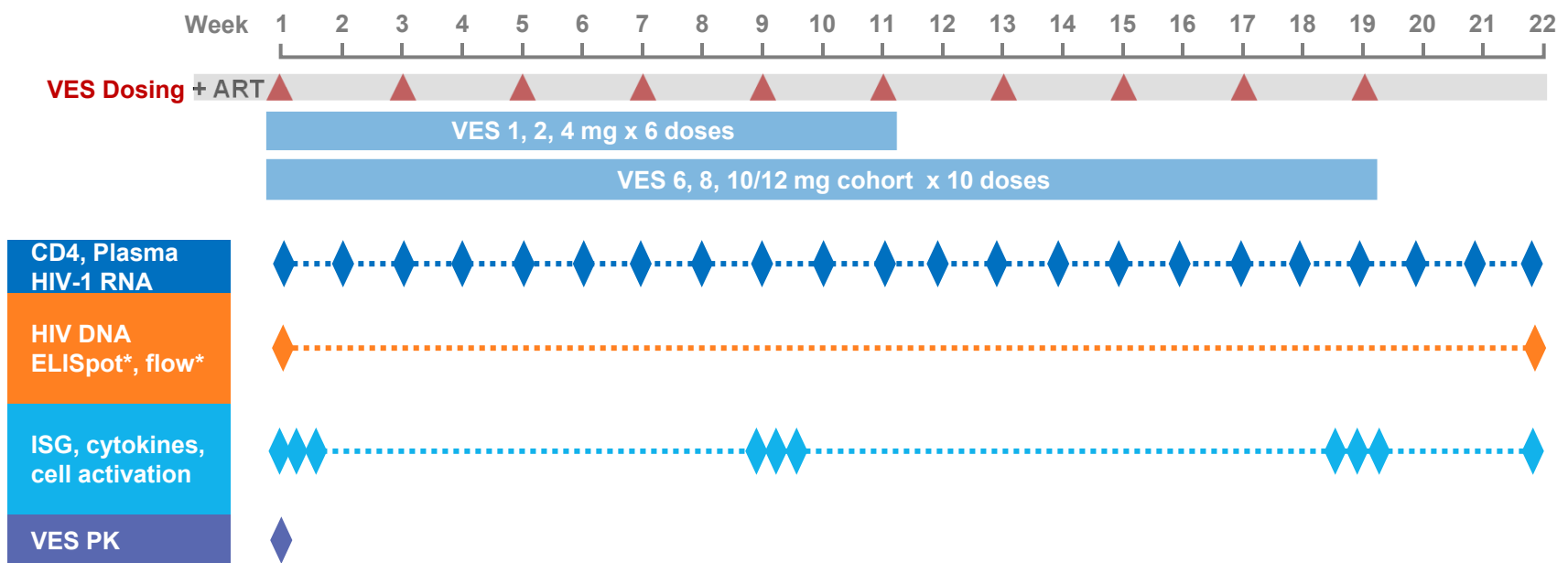
Acknowledgments

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



*Measurement of HIV specific T-cell responses

Baseline Demographic and Disease Characteristics

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

Dx, diagnosis.

Laboratory Abnormalities

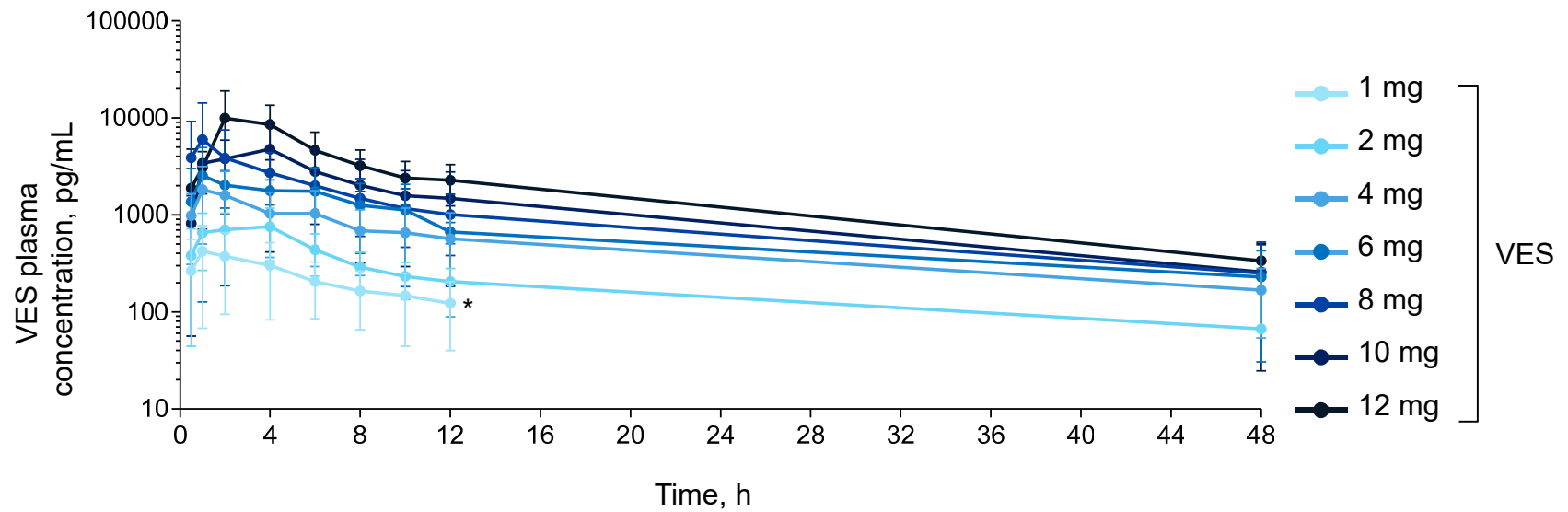
Participants, n (%)	PBO n=12	1 mg n=6	2 mg n=6	4 mg n=6	6 mg n=6	8 mg n=6	10/12 mg n=6
Grade 1	7 (58)	5 (83)	5 (83)	3 (50)	3 (50)	3 (50)	3(50)
Grade 2	2 (17)	1 (17)	0	1 (17)	2 (33)	2 (33)	1 (17)
Grade 3	0	0	0	0	0	0	1 (17) ^a
Grade 4	0	0	0	0	0	1 (17) ^b	1 (17) ^b

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

^a Participant with hematuria with confirmed menses; ^b Participants with elevated creatinine kinase due to strenuous exercise

◆ No dose dependent trends in lab abnormalities

Pharmacokinetics



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

*Below limit of quantification at 48 hours