

GS-8588, A Novel Envelope-Targeting Bispecific T-Cell Engager for HIV Cure

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GS-8588 study



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Conclusions

- GS-8588 is a novel bispecific T-cell engager (TCE) that mediates potent, broad, and specific killing of cluster of differentiation 4 (CD4) T cells infected with a diverse panel of HIV clinical isolates in vitro
- GS-8588 induces low-level T-cell activation and cytokine secretion when incubated with peripheral blood mononuclear cells (PBMCs) from people with HIV (PWH) ex vivo
- GS-8588 exhibits IgG-like pharmacokinetics (PK), with ~25% lymph node to serum exposure ratio in a nonhuman primate (NHP) model
- No adverse findings were observed in good laboratory practice (GLP) cynomolgus toxicology studies when GS-8588 was dosed to 100 mg/kg
- These results support the clinical evaluation of GS-8588 as a therapeutic candidate for the elimination of latent HIV-infected cells in PWH

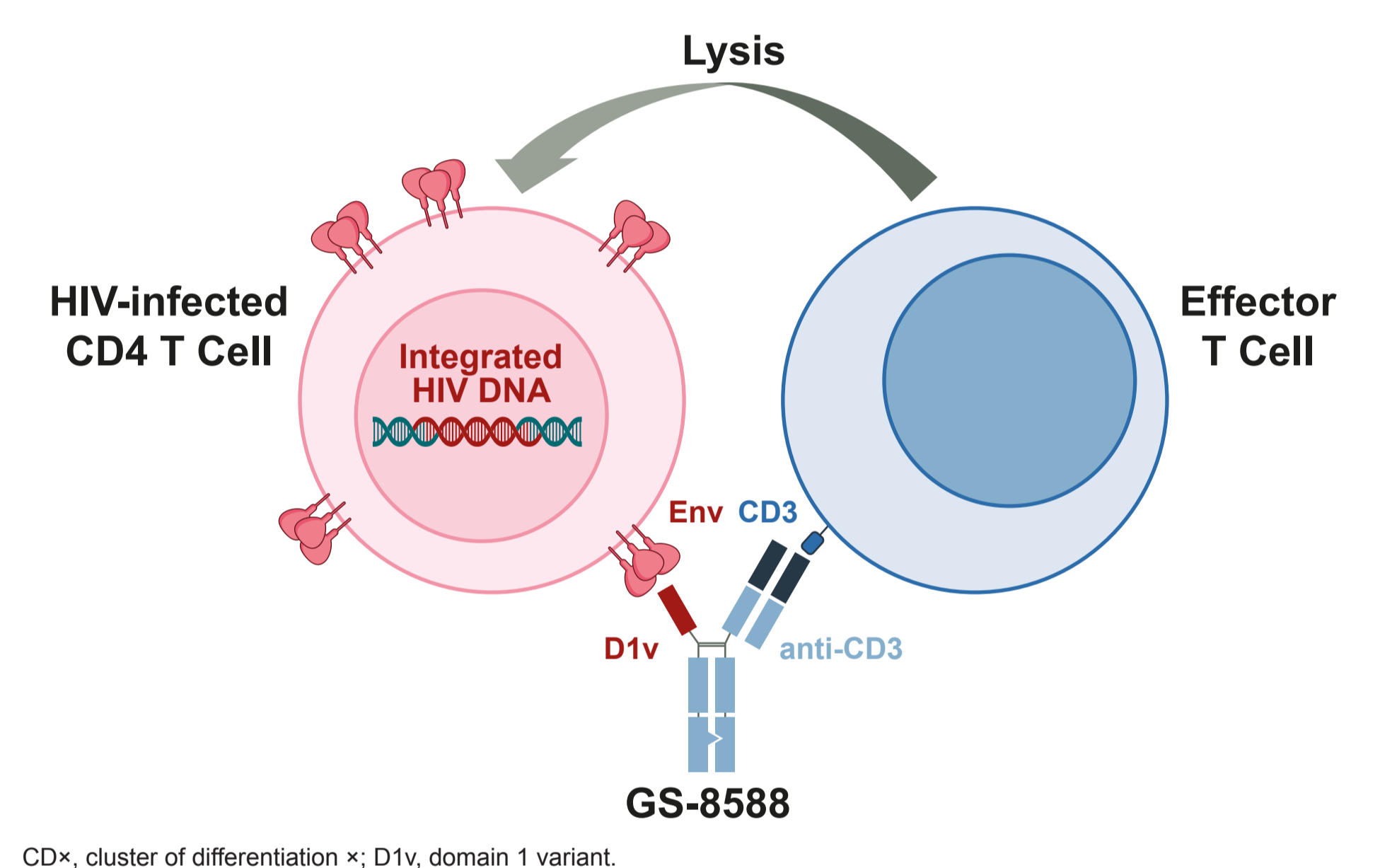
Plain Language Summary

- Current antiretroviral therapy (ART) helps PWH by stopping the virus from replicating in the body. However, it cannot completely cure the disease because there are some HIV-infected cells that are hidden in the body, and these cells can cause the virus to come back if ART is stopped¹
- GS-8588 is a novel antibody-like protein designed to recruit one's own immune cells to kill HIV-infected cells
- In this study, we examined how well GS-8588 can destroy HIV-infected cells in laboratory cell systems. We also studied how the body absorbs and processes GS-8588, as well as its safety, using cynomolgus monkeys as a model
- We showed that GS-8588 kills HIV-infected cells effectively, and it is well tolerated by cynomolgus monkeys at doses higher than the predicted dose that would be used to treat people
- GS-8588 is currently being evaluated in a phase 1 clinical trial in PWH who have the virus under control with ART

Introduction

- A functional cure for HIV requires therapeutic interventions that can eliminate reservoirs of integrated proviruses in CD4 T cells
- GS-8588 is a novel bispecific TCE designed to redirect polyclonal effector T cells to kill HIV-infected, envelope (Env)-expressing CD4 T cells (Figure 1)
- GS-8588 consists of an engineered CD4 domain 1 variant (D1v) that exhibits improved Env-targeting potency and developability profile,² a humanized anti-CD3 Fab, and an effector-silent human IgG1 hetero-Fc
- Here, we characterize GS-8588 for its binding and killing activities in vitro, T-cell activation and cytokine release ex vivo, and PK and toxicology profiles in NHP

Figure 1. GS-8588 Mechanism of Action

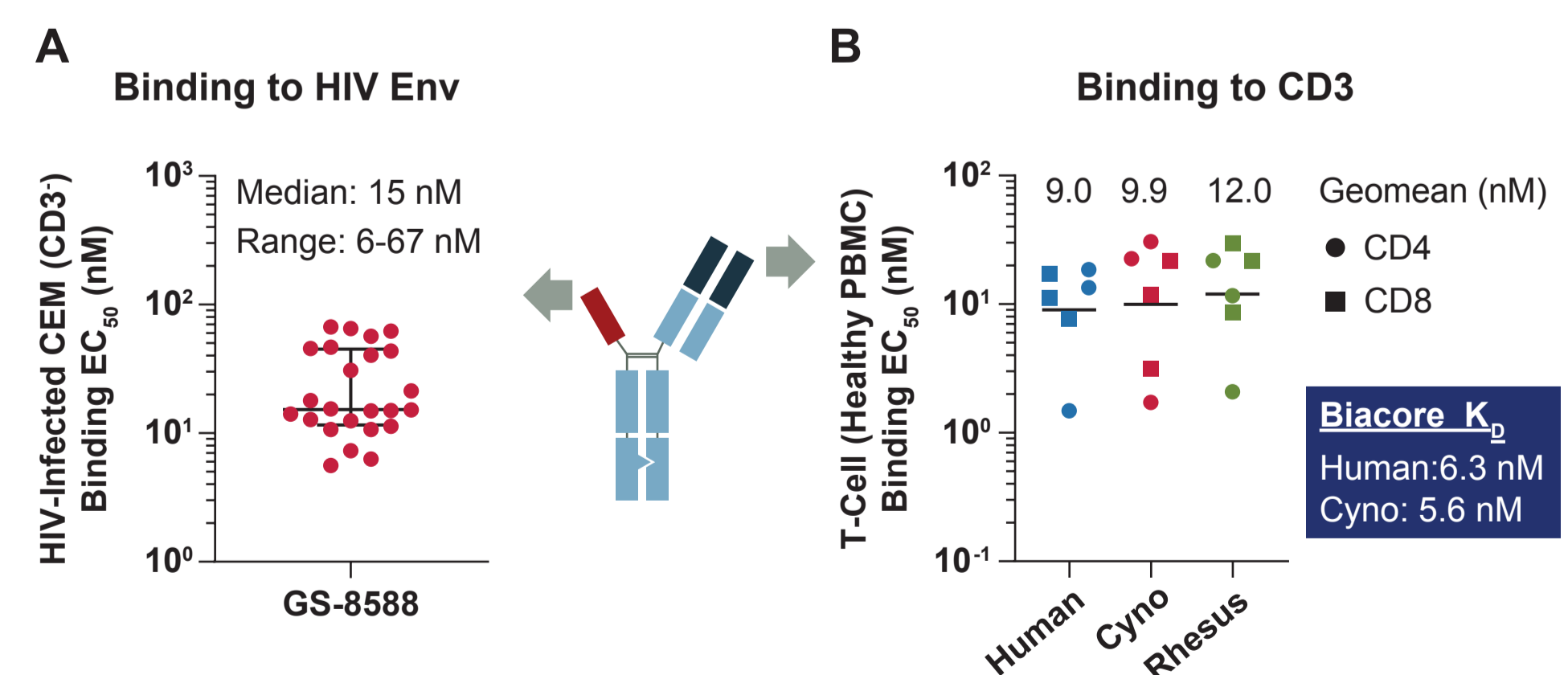


Methods

- Binding to Env or CD3 was evaluated in vitro by incubating GS-8588 dilution series with HIV-infected CEM (a T-lymphoblast cell line) or PBMCs from healthy donors, respectively
- Specific killing was evaluated in vitro by incubating GS-8588 dilution series with HIV-infected target cells (resting or activated primary CD4 T cells, or CEM cells) and PBMC effector cells; off-target killing of major histocompatibility complex class II (MHCII)-expressing B cells was assessed in the same assay
- T-cell activation and cytokine secretion were monitored ex vivo in GS-8588-treated PBMC samples derived from PWH
- PK of GS-8588 was evaluated in cynomolgus monkeys at a single 1 mg/kg intravenous dose
- Lymph node to serum exposure ratio of GS-8588 was evaluated in cynomolgus monkeys at a single 10 mg/kg intravenous dose
- Safety and tolerability of GS-8588 were evaluated in a cynomolgus monkey GLP toxicology study at 5 weekly doses up to 100 mg/kg/week

Results

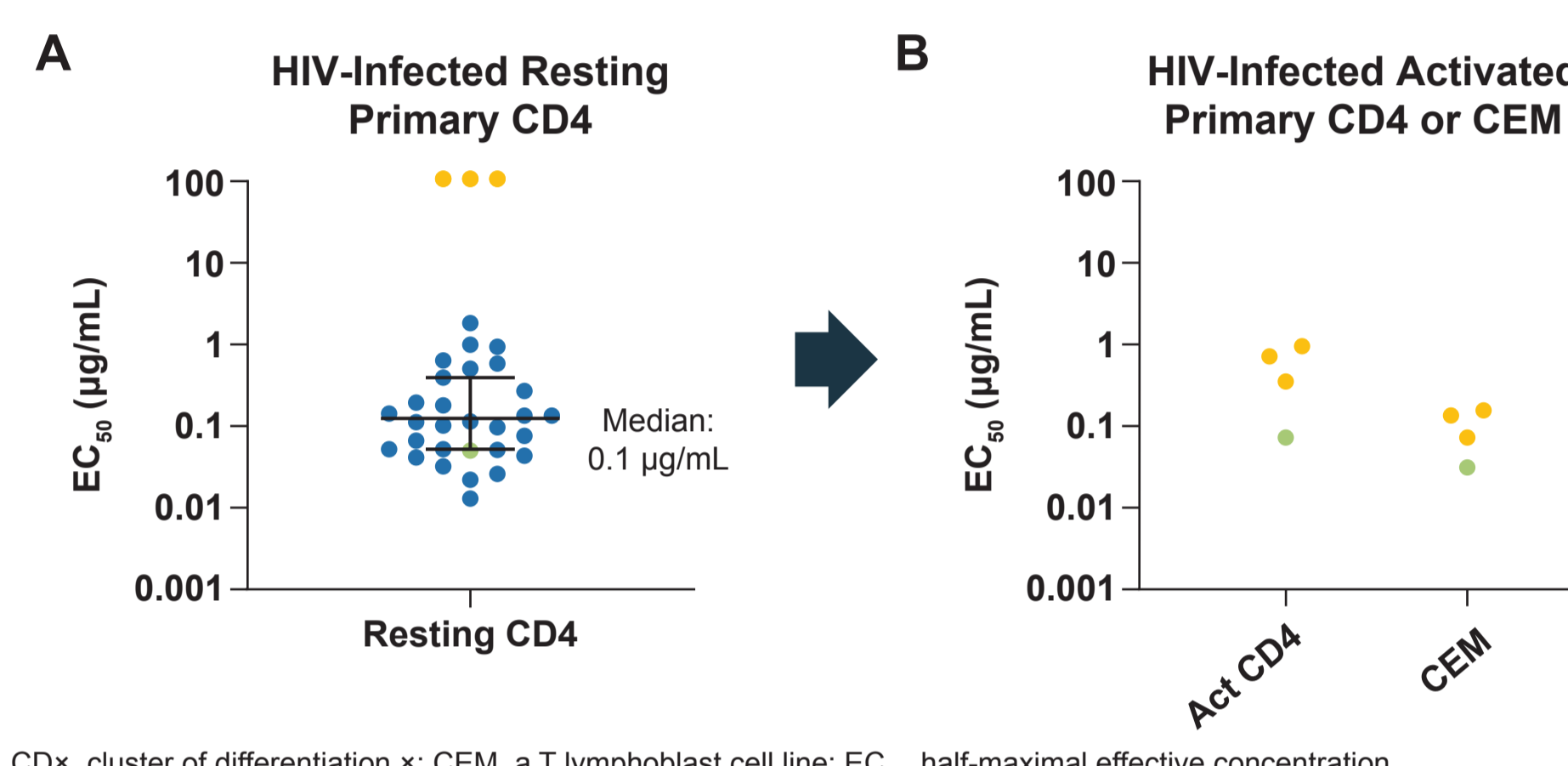
Figure 2. GS-8588 Binds to Cell Surface Env and CD3



- GS-8588 binds to HIV-infected CEM cells (CD3-negative) with half-maximal effective concentration (EC₅₀) values ranging from 6 to 67 nM across 24 clade B clinical isolates (Figure 2A)
- GS-8588 binds to healthy CD4 and CD8 T cells from human, cynomolgus, and rhesus monkeys with similar potency (Figure 2B)

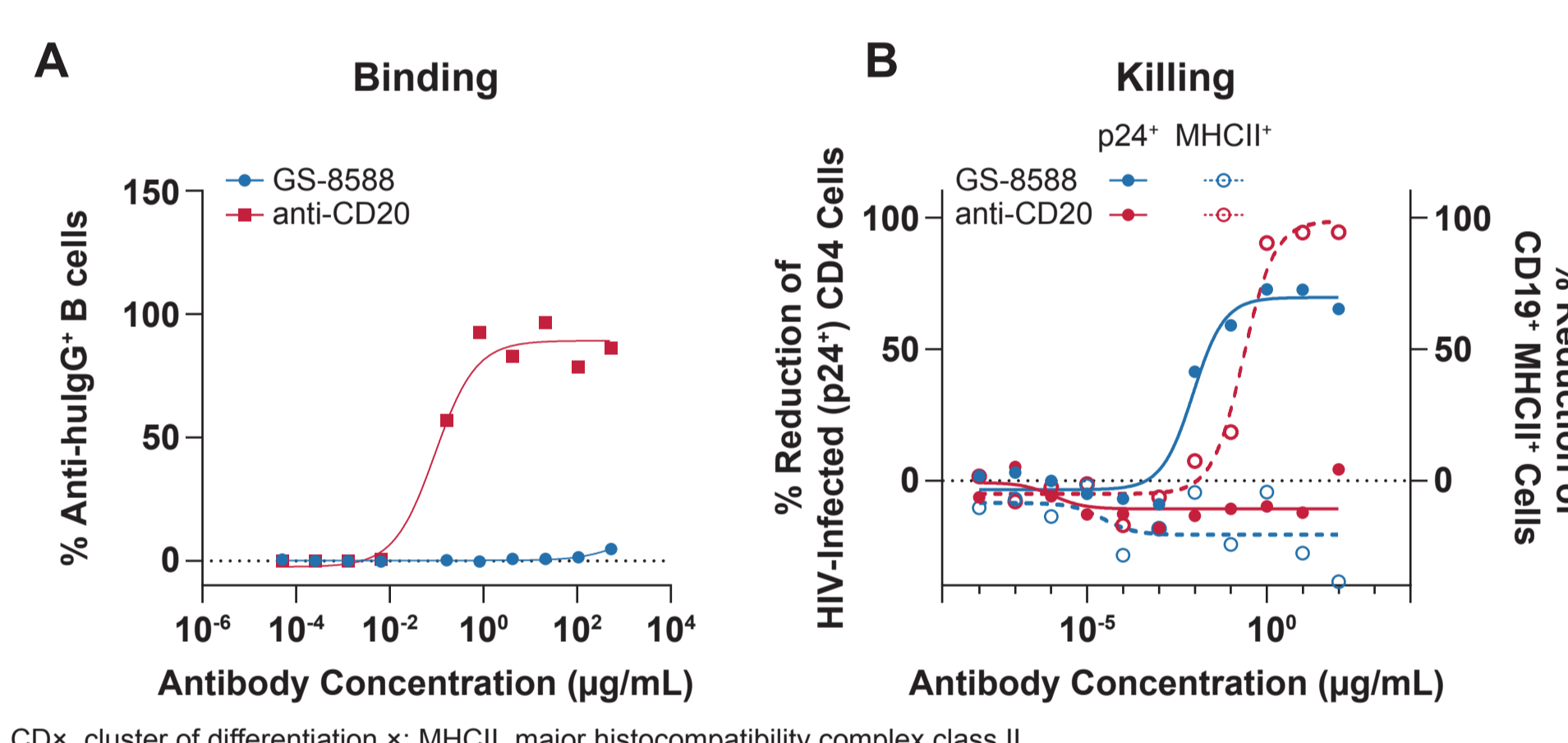
Results

Figure 3. GS-8588 Mediates Potent and Broad Killing of HIV-Infected CD4 Cells



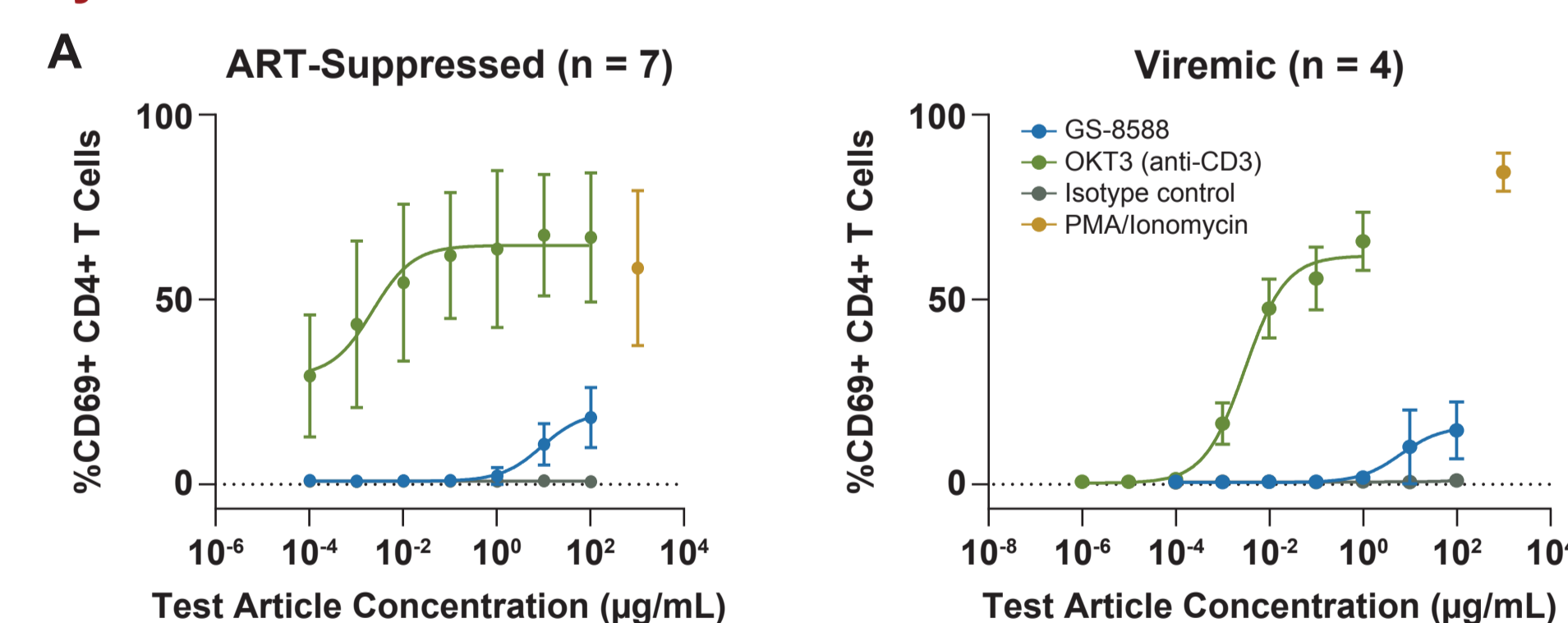
- GS-8588 mediated killing of resting primary CD4 T cells infected with 29 of the 32 HIV-1 isolates tested (median EC₅₀ 0.1 µg/mL) (Figure 3A)
- For the 3 remaining isolates, GS-8588-mediated killing was observed in activated PBMC-based and CEM-based killing assays (Figure 3B)

Figure 4. GS-8588 Exhibits No Detectable Binding or Killing of MHCII-Expressing B Cells



- GS-8588 exhibits no detectable binding to B cells (Figure 4A)
- GS-8588 mediated killing of HIV-infected CD4 cells, and not CD19⁺ MHCII⁺ B cells, in the same assay well (Figure 4B)

Figure 5. GS-8588 Mediates Low-Level T-Cell Activation and Cytokine Release Ex Vivo

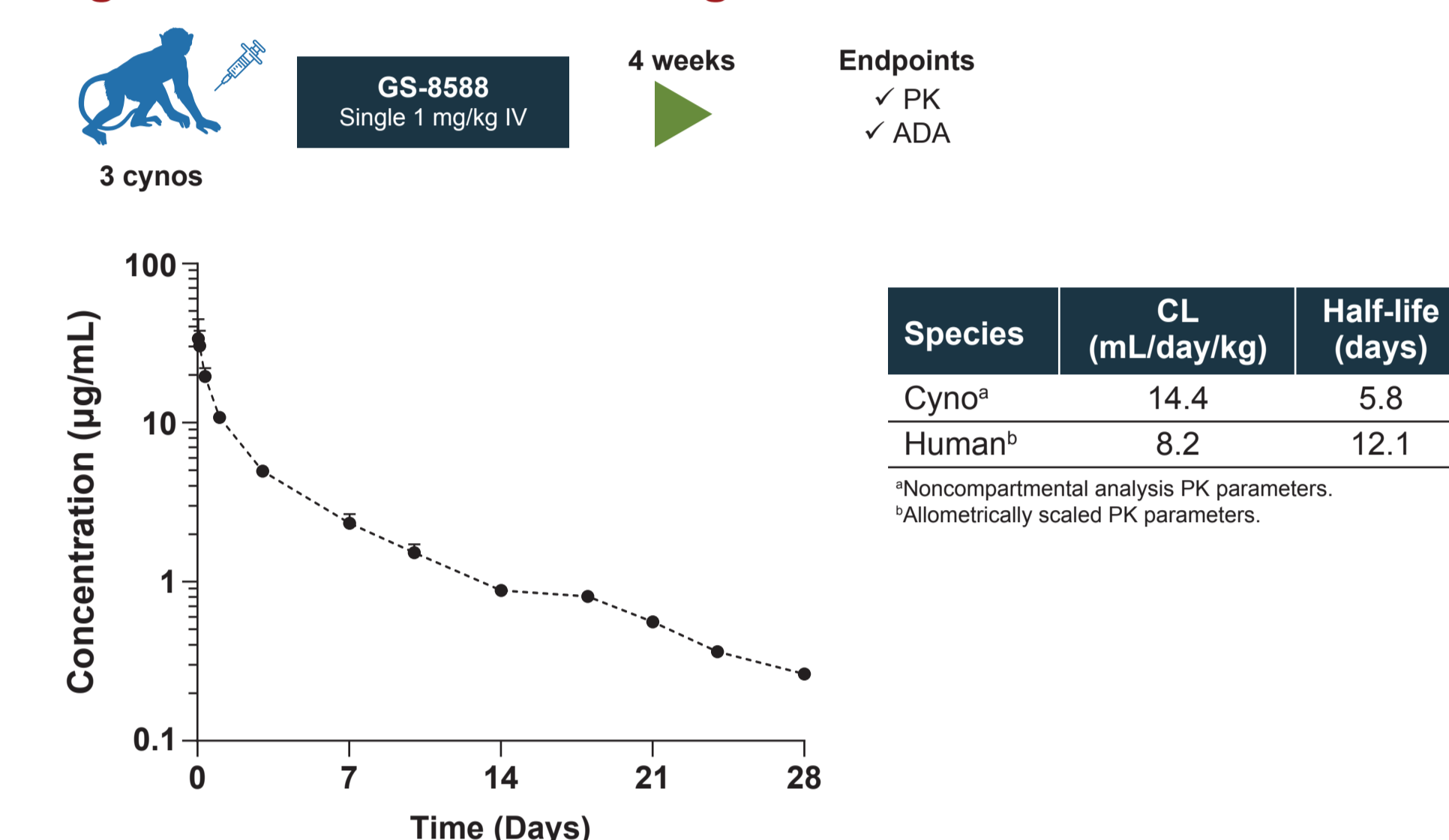


Cytokine	ART-Suppressed (n = 4)			Viremic (n = 4)		
	GS-8588	Isotope Control	PMA/ionomycin	GS-8588	Isotope Control	PMA/ionomycin
IFN-γ	7.6	0.5	1756.4	52.0	15.6	6003.7
TNF-α	22.9	5.3	3270.3	9.5	6.9	256.6
IL-6	3.0	2.6	6266.2	35.3	45.0	1157.8
IL-2	3.5	2.8	8814.6	7.8	8.1	2846.9
IL-4	2.9	1.8	22.9	12.4	11.4	21.7
IL-10	0.7	0.3	2.9	12.3	11.9	18.0

*Mean concentration of cytokines measured for supernatants from PBMCs treated with 100 µg/mL of GS-8588, isotope control (GS-832677), and 50 ng/mL and 0.5 µg/mL of PMA/ionomycin combination. ART, antiretroviral therapy; CDx, cluster of differentiation x; IFN, interferon; IL, interleukin; PMA, phorbol myristate acetate; PBMC, peripheral blood mononuclear cell; PMA, phorbol myristate acetate; PWH, people with HIV; TNF, tumor necrosis factor.

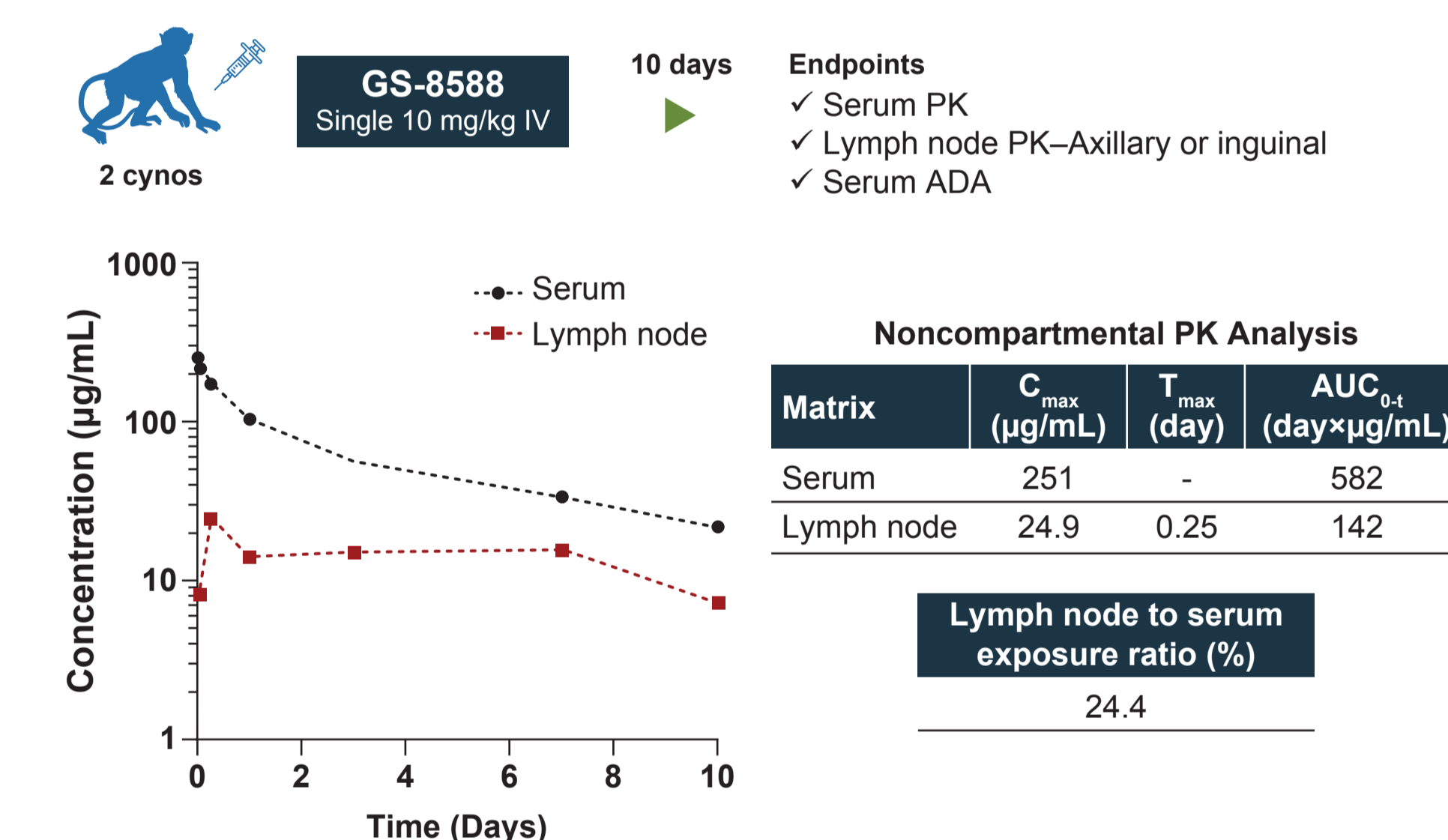
- GS-8588 induces low-level CD69 upregulation (geometric mean EC₁₀ ≥ 10.3 µg/mL) when co-incubated with PBMCs derived from ART-suppressed (n = 7) and viremic (n = 4) PWH; EC₁₀ is defined as GS-8588 concentration corresponding to 10% CD69⁺ T cells (Figure 5A)
- GS-8588 induces low-level cytokine production (mean maximum signals ≤ 52 pg/mL) in the supernatant (Figure 5B)

Figure 6. GS-8588 Exhibits IgG-Like Serum PK in NHP Model



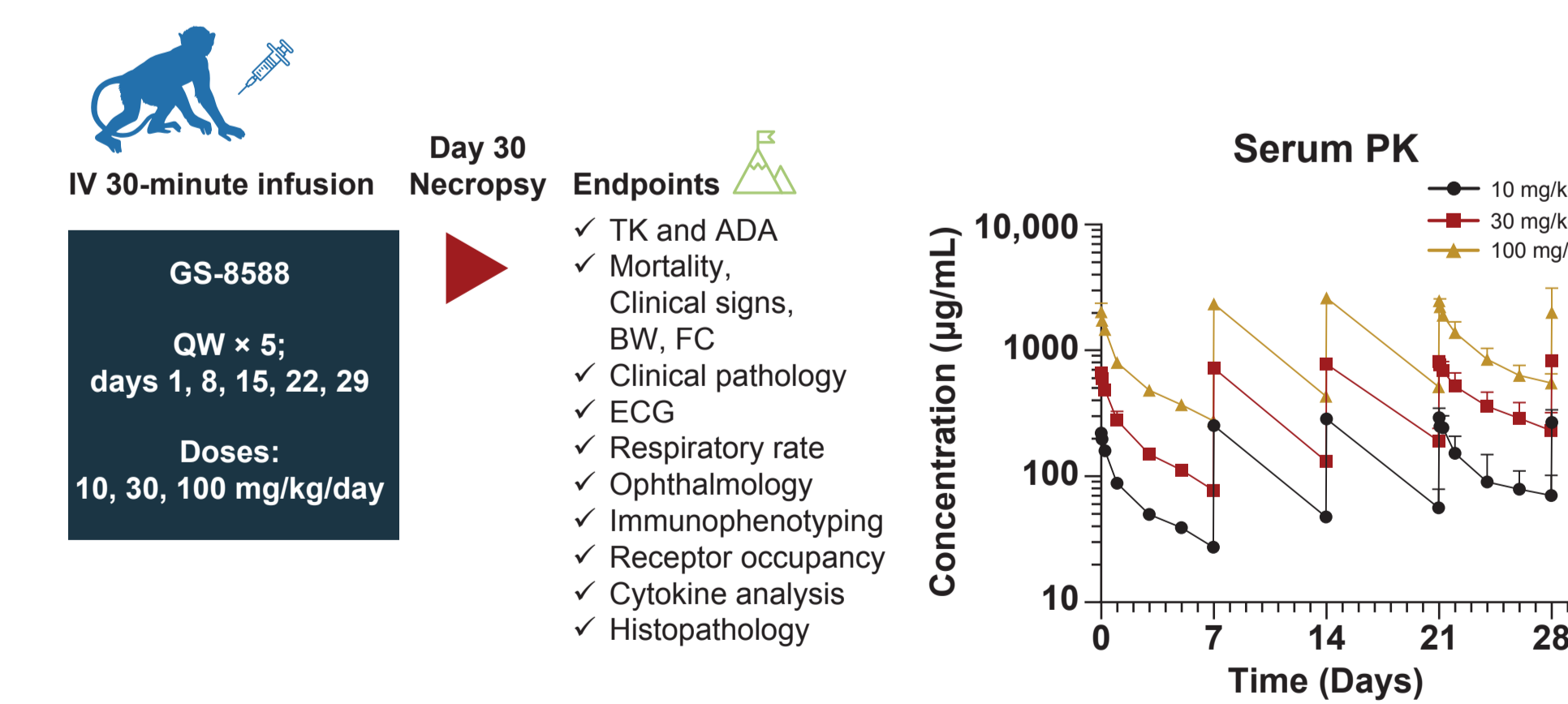
- GS-8588 exhibits a typical biphasic serum PK profile, with a projected ~12-day half-life in humans (Figure 6)
- Antidrug antibodies (ADAs) were detected and had minimal impact on PK in 2 of 3 cynomolgus at ≥ 24 days

Figure 7. GS-8588 Lymph Node to Serum Exposure Ratio Is ~25%



- Lymphoid tissues are the predominant sites of HIV reservoirs³
- Based on AUC₀₋₁₀, a lymph node to serum exposure ratio of ~25% was calculated (Figure 7)
- This exposure ratio and in vitro killing data were used to estimate the minimal efficacious dose

Figure 8. No Adverse Findings in GLP Cynomolgus Toxicology Study up to 100 mg/kg



- GS-8588 was well tolerated at all dose levels with no mortality or adverse findings (Figure 8)
- Dose-proportional serum PK was observed (Figure 8)
- Estimated margins were > 100-fold, based on initially projected minimally efficacious dose

References: 1. Chun TW, et al. *Nat Immunol*. 2015;16:584-9. 2. Chen W, et al. *J Virol*. 2014;88:1125-39. 3. Banga R, et al. *Curr Opin HIV AIDS*. 2024;19:116-23.

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Disclosures: All authors were employed at Gilead Sciences when this work was conducted.

Abbreviations: ADA, antidrug antibody; ART, antiretroviral therapy; AUC, area under the curve; CDx, cluster of differentiation x; CEM, a T lymphoblast cell line; C_{max}, maximum plasma concentration; Cyno, cynomolgus; D1v, domain 1 variant; EC₅₀, half-maximal effective concentration; Env, envelope; Fab, fragment antigen-binding; FC, food consumption; GLP, good laboratory practice; IFN, interferon; IL, interleukin; MHCII, major histocompatibility complex class II; NHP, nonhuman primate; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetics; PMA, phorbol myristate acetate; PWH, people with HIV; TCE, T-cell engager; TK, toxicokinetics; T_{max}, time to maximum concentration; TNF, tumor necrosis factor.