Safety and Immunogenicity of GS-1966+GS-1144 Vaccines in Virally Suppressed Adults Living With HIV-1: A Phase 1b, Randomized, Placebo-Controlled Study

P211

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Conclusions

- GS-1966+GS-1144 was safe and well tolerated in this first-in-human study of a novel therapeutic HIV-1 T-cell vaccine in people with HIV (PWH) on antiretroviral therapy (ART)
- There was no significant difference in vaccine-specific T-cell response by interferon-gamma (IFNγ) enzyme-linked ImmunoSpot (ELISpot) between vaccine recipients and placebo recipients in this analysis
  - Cohort 3 recipients of the bivalent vaccine had the largest peak and change from baseline to peak T-cell responses
- Pre-existing vaccine-specific T-cell responses were observed in all cohorts, though these responses were consistent with what has been observed previously in PWH[1-4]
  - The analytic approaches utilized did not distinguish if GS-1966+GS-1144 was able to boost pre-existing responses or may have induced de novo T-cell responses in cohort 3
- Further investigations are underway into additional metrics of T-cell functionality that may provide more insight into the impact of GS-1966+GS-1144, including evaluation of T-cell breadth and T-cell polyfunctionality
- Future studies are needed to optimize therapeutic vaccine strategies for HIV cure. Combination approaches are likely needed to both reduce viral reservoir and enhance vaccine responses through immune modulation

Plain Language Summary

- As a key component of a future HIV cure, new vaccines are being developed (HIV T-cell vaccine) that can enhance the immune system's T cells, which fight infections like HIV
- In this study, researchers evaluated one such investigational HIV T-cell vaccine called GS-1966+GS-1144 for its safety and immunological activity, in people with HIV who are using antiretroviral therapy
- The study monitored 34 people in 3 cohorts who received the vaccine at different doses and versions, and 15 people who received a placebo, for 48 weeks
- Results showed that the vaccine was generally safe and well tolerated, with most people experiencing mild to moderate, short-lived flu-like symptoms. Vaccinated individuals from cohort 3 who received the bivalent vaccine showed higher T-cell activity than those who received placebo, but the difference was not statistically significant

Background

- Therapeutic vaccination to enhance HIV-specific T-cell immunity may be a crucial component of a future combination HIV cure or long-term remission strategy[5]
- A novel heterologous prime/boost vaccine regimen comprising a chimpanzee adenoviral vector (ChAdV) prime and self-amplifying messenger RNA (samRNA) formulated in lipid nanoparticles (LNPs) was previously shown to induce robust and broad antigen-specific T-cell responses in a preclinical non-human primate model and in ongoing oncologic clinical trials[6,7]
- GS-1966+GS-1144 is a heterologous vaccine regimen containing GS-1966, a ChAdV, and GS-1144, a samRNA-LNP, which both encode a novel conserved element HIV-1 immunogen spanning Gag, Pol, and Nef

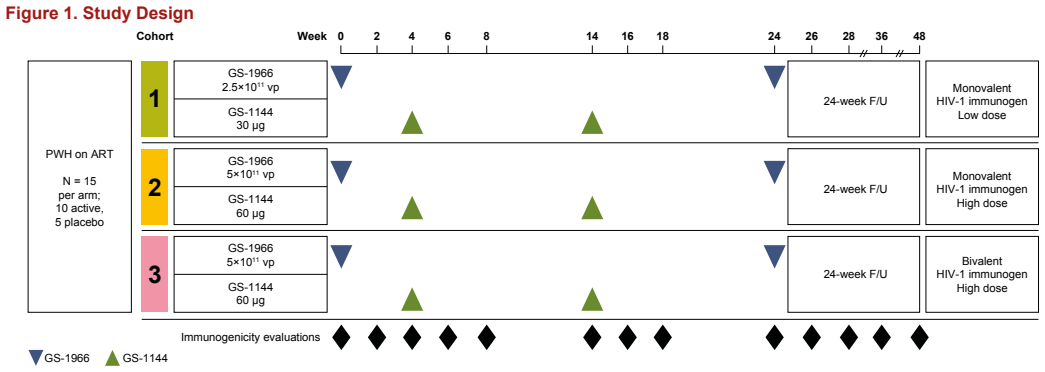
Objective

- To evaluate the safety, tolerability, and immunogenicity of GS-1966+GS-1144 HIV vaccine regimens in virologically suppressed PWH (clade B) on ART

Materials and Methods

- This was a single-blind, placebo-controlled, randomized trial conducted at 5 sites in the United States (**Figure 1**)
  - Inclusion/exclusion criteria included age 18-60 years, plasma HIV-1 RNA levels < 50 copies/mL for ≥ 12 consecutive months prior to and at screening, and CD4+ T-cell count > 350 cells/μL
- Three cohorts of participants were randomized 2:1 to receive GS-1966+GS-1144 or placebo
- Two doses of GS-1966+GS-1144 were evaluated. Cohorts 1 (low dose) and 2 (high dose) received a monovalent HIV-1 immunogen; cohort 3 (high dose) received a bivalent version
  - Participants maintained their fully suppressive ART regimens
- Immunogenicity was evaluated longitudinally by IFNγ ELISpot assay using 4 peptide pools spanning the bivalent vaccine immunogen sequence (Gag, Nef, Pol-1, and Pol-2)
- The primary end point was safety, measured by the incidence of adverse events (AEs) and graded clinical laboratory abnormalities
- The secondary end point was immunogenicity, measured by the magnitude of the total vaccine-specific HIV-1-specific T-cell response. Statistical significance was evaluated for peak and change from baseline to peak vaccine-specific T-cell responses by van Elteren test stratified by cohort

Figure 1. Study Design



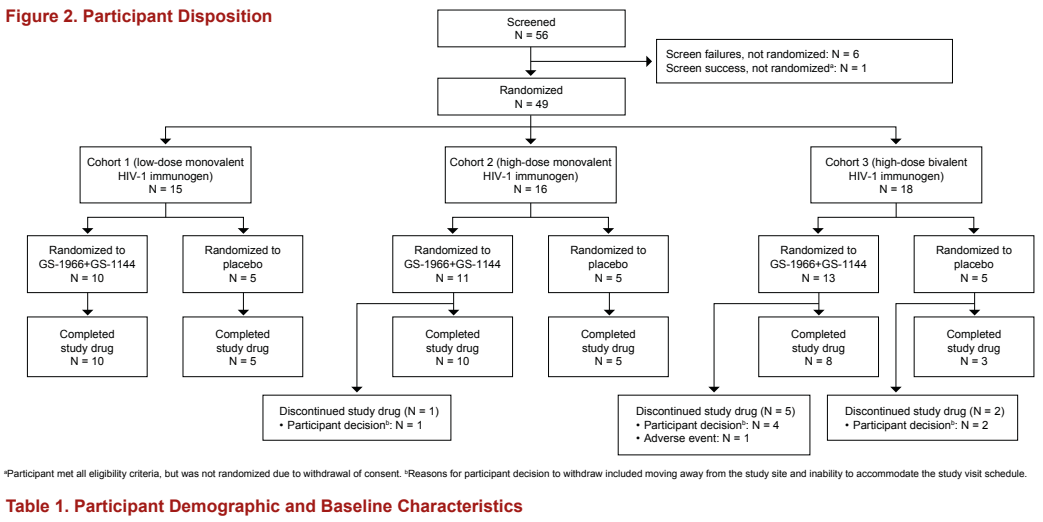
ART, antiretroviral therapy; F/U, follow-up; PWH, people with HIV; vp, viral particles.

Results

Participant Disposition and Characteristics

- The 49 participants enrolled included 45 males and 4 females with median (Q1, Q3) age 40 (33, 51) years and 10 (6, 17) years since HIV diagnosis (**Figure 2, Table 1**)

Figure 2. Participant Disposition



[a]Participant met all eligibility criteria, but was not randomized due to withdrawal of consent. [b]Reasons for participant decision to withdraw included moving away from the study site and inability to accommodate the study visit schedule.

Table 1. Participant Demographic and Baseline Characteristics

	All Cohorts		
	GS-1996+GS-1144 (n = 34)	Placebo (n = 15)	Overall (N = 49)
Age, years			
Mean (SD)	43 (10)	40 (12)	42 (10)
Median (Q1, Q3)	42 (33, 51)	36 (28, 52)	40 (33, 51)
Sex at birth, n (%)			
Male	30 (88)	15 (100)	45 (92)
Female	4 (12)	0	4 (8)
Race, n (%)			
Asian	0	1 (7)	1 (2)
Black or African American	10 (29)	4 (27)	14 (29)
White	23 (68)	8 (53)	31 (63)
Other	1 (3)	1 (7)	2 (4)
Not stated	0	1 (7)	1 (2)
Ethnicity, n (%)			
Not Hispanic or Latino/a	19 (56)	7 (47)	26 (53)
Hispanic or Latino/a	15 (44)	8 (53)	23 (47)
Baseline HIV-1 RNA categories, copies/mL			
< 50	34 (100)	15 (100)	49 (100)
Baseline CD4 cell count, cells/μL			
Mean (SD)	828 (221)	759 (178)	807 (210)
Median (Q1, Q3)	799 (697, 976)	684 (620, 886)	761 (649, 915)
Years since HIV diagnosis			
Mean (SD)	13 (9)	10 (7)	12 (9)
Median (Q1, Q3)	10 (6, 17)	10 (4, 17)	10 (6, 17)

Safety of GS-1966+GS-1144

- No serious AEs occurred (**Table 2**)
- Treatment was discontinued in 1 participant who experienced grade 2 (nonserious) Bell's palsy, which resolved in 14 days
- The most common treatment-emergent AEs were mild to moderate injection-site reactions and transient flu-like symptoms (**Table 3, Table 4**)
- Transient decreases in lymphocyte counts were observed 1 day after administration of either vaccine and resolved within 2 weeks without associated clinical sequelae

Table 2. Summary of Treatment-Emergent Adverse Events

	GS-1966+GS-1144 (n = 34)	Placebo (n = 15)
TEAEs, n (%)	34 (100)	13 (87)
Related	34 (100)	8 (53)
Grade 3-4 AEs, n (%)	10 (29)	0
Related	8 (24)	0
SAEs, n (%)	0	0
AEs leading to study drug discontinuation, n (%)	1 (3)	0
AEs leading to study drug interruption, n (%)	0	0
Deaths, n (%)	0	0

Severity grades were defined by the DAIDS table for grading the severity of adult and pediatric adverse events (corrected v2.1, July 2017).
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 3. Treatment-Emergent Adverse Events Reported for > 2 Participants Overall by Preferred Term

Preferred Term	GS-1966+GS-1144 (n = 34)	Placebo (n = 15)
Participants with any TEAE, n (%)	34 (100)	13 (87)
Fatigue	33 (97)	5 (33)
Injection-site pain	33 (97)	4 (27)
Myalgia	30 (88)	6 (40)
Headache	30 (88)	5 (33)
Malaise	31 (91)	2 (13)
Pyrexia	31 (91)	2 (13)
Arthralgia	25 (74)	5 (33)
Nausea	19 (56)	1 (7)
Injection-site swelling	11 (32)	1 (7)
Chills	9 (27)	0
COVID-19	4 (12)	3 (20)
Injection-site erythema	5 (15)	0
Injection-site induration	5 (15)	0
Night sweats	3 (9)	0
Pain	3 (9)	0

TEAE, treatment-emergent adverse event.

Table 4. Grade 3 Treatment-Emergent Adverse Events by Preferred Term

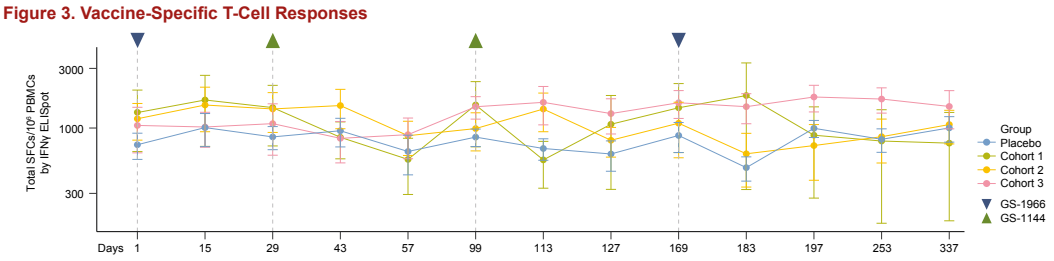
Preferred Term	GS-1966+GS-1144 (n = 34)	Placebo (n = 15)
Participants with grade 3 or higher TEAE,[b,c] n (%)	10 (29)	0
Pyrexia	6 (18)	0
Fatigue	4 (12)	0
Headache	3 (9)	0
Injection site pain	3 (9)	0
Malaise	3 (9)	0
Myalgia	3 (9)	0
Arthralgia	2 (6)	0
Blood creatine phosphokinase increased	2 (6)	0
Chills	2 (6)	0

[a]Severity grades were defined by the DAIDS table for grading the severity of adult and pediatric adverse events (corrected v2.1, July 2017). [b]No grade 4 adverse events were observed. [c]Participants could have more than 1 adverse event.
TEAE, treatment-emergent adverse event.

GS-1966+GS-1144 Immunogenicity

- Pre-existing vaccine-specific T-cell responses were detected in all cohorts (**Figure 3, Figure 4**)
- No significant differences in median peak vaccine-specific T-cell responses were found between cohorts or compared with placebo
  - Cohort 3 had the numerically largest change from baseline to peak T-cell response

Figure 3. Vaccine-Specific T-Cell Responses

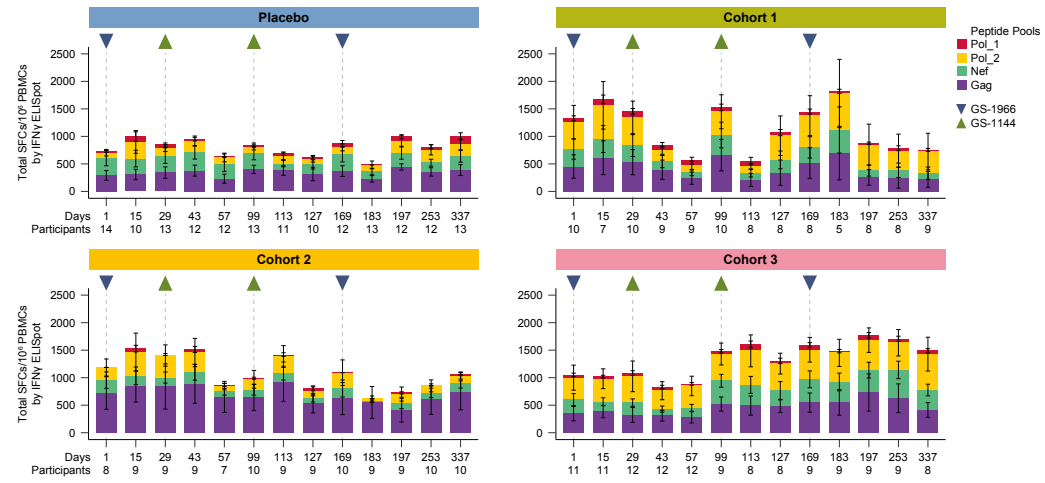


Mean ± standard error of mean.

Immunogenicity, SFCs/10⁶ PBMCs	Placebo	Cohort 1	Cohort 2	Cohort 3	*P* value[a]
Peak, median (min, max)	1846 (605, 3172)	1169 (4, 8484)	1254 (175, 5672)	1860 (404, 5920)	0.53
Change from baseline to peak, median (min, max)	740 (86, 2848)	647 (0, 1612)	526 (0, 2888)	986 (400, 2490)	0.49

Assay: validated IFNγ ELISpot (4 peptide pools); only participants with data for all 4 peptide pools are reported. Samples collected pre-dose at vaccination timepoints.
[a]*P* value by van Elteren test stratified by cohort.
ChAdV, chimpanzee adenovirus vector; IFNγ ELISpot, interferon-gamma enzyme-linked ImmunoSpot; PBMC, peripheral blood mononuclear cell; samRNA, self-amplifying messenger RNA; SFC, spot-forming cell.

Figure 4. Vaccine-Specific T-Cell Responses by Peptide Pools



Mean ± standard error of mean.

Assay: validated IFNγ ELISpot (4 peptide pools); only participants with data for all 4 peptide pools are reported. Samples collected pre-dose at vaccination timepoints.
ChAdV, chimpanzee adenovirus vector; IFNγ ELISpot, interferon-gamma enzyme-linked ImmunoSpot; PBMC, peripheral blood mononuclear cell; samRNA, self-amplifying messenger RNA; SFC, spot-forming cell.

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