Resistance and Pharmacokinetic/Pharmacodynamic Analyses of GS-1720, a Once-Weekly Oral Integrase Strand Transfer Inhibitor

P035

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Conclusions

- No observed cases of emergent integrase (IN) resistance occurred after GS-1720 monotherapy treatment in this Phase 1b proof-of-concept study
- GS-1720 showed robust antiviral activity (≥1.5 log_{10} copies/mL decline in HIV-1 RNA from baseline) at Day (D) 11 concentrations above inhibitory quotient (IQ) 2
- The pharmacokinetics (PK)/pharmacodynamics (PD) data and lack of observed resistance support further clinical development
- An oral combination regimen of once-weekly GS-1720 and GS-4182[a] is being evaluated in Phase 2 studies among virologically suppressed and treatment-naïve people with HIV-1 (PWH)[b]

Plain Language Summary

- GS-1720 is a medicine that is being studied to treat HIV, but it is not yet approved for people to take outside of a clinical trial
  - GS-1720 can be taken just once a week unlike many other HIV medicines that need to be taken every day
- We tested many doses of GS-1720 in people with HIV to see how well it works and to study if the HIV virus developed any changes that helped It resist the effects of GS-1720 (called treatment resistance)
- We found that GS-1720 worked well to treat HIV, and people who took GS-1720 did not develop resistance to this medicine
- We are planning more studies to test if GS-1720 combined with another drug called GS-4182 can be taken once a week to treat people with HIV

Background

- Adherence to HIV-1 treatment reduces the risk of virologic failure, yet can be challenging; an unmet need for long-acting antiretroviral therapies (ART) remains[1,2]
- GS-1720 is an oral integrase strand transfer inhibitor (INSTI) with potent anti-HIV-1 activity and a median half-life of 9.3 days, supportive of weekly dosing[3]
- In a Phase 1b study in PWH, GS-1720 resulted in a mean decline in HIV-1 RNA from baseline to D11 of >2 log_{10} copies/mL in three of the four GS-1720 dose cohorts, with a 1.74 log_{10} copies/mL decline observed in the lowest dose cohort[4]

Objective

- To assess GS-1720 resistance and PK/PD from the current Phase 1b study

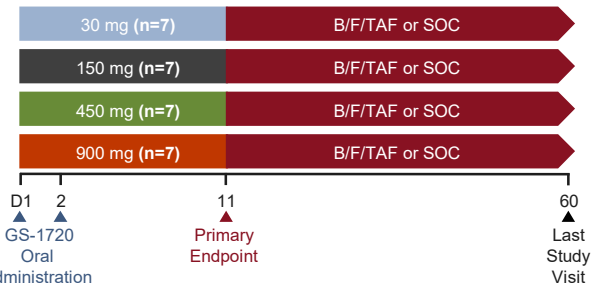
Methods

- This Phase 1b, open-label, multicohort substudy enrolled PWH[c]
- Participants with detectable HIV-1 viral load were enrolled into four cohorts (n=7/cohort) and administered oral GS-1720 on D1 and D2, then switched on D11 to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) or an alternative standard of care (SOC) ART regimen (**Figure 1**)
- Participants were tested for genotypic and phenotypic IN resistance at baseline (screening visit) and D11 using the GeneSeq® Integrase[d] and PhenoSense® Integrase[e] assays[f]
  - Participants with suboptimal virologic response (SVR) after D11, defined as HIV-1 RNA ≥50 copies/mL and <1 log_{10} HIV-1 RNA reduction from D11, qualified for further genotypic and phenotypic resistance testing
- Intensive PK sampling was collected on D1 and D2 up to 12 hours post-dose, followed by single anytime plasma PK sampling throughout the study
- GS-1720 plasma concentrations were quantified using a validated high-performance liquid chromatography-tandem mass spectrometry bioanalytical method

Figure 1. Study Design

Key eligibility criteria:

- Aged 18–65 years
- HIV-1 RNA 5000–≤400,000 cpm
- CD4+ T-cells >200 cells/µL
- Treatment naïve *OR* treatment experienced, but naïve to INSTIs and off ART for ≥12 weeks



ART, antiretroviral therapy; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; cpm, copies/mL; D, day; INSTI, integrase strand transfer inhibitor; SOC, standard of care.

Results

Study Population

- Twenty-eight participants were enrolled
- Median (range) age was 33 (18–62) years, and 10.7% were female (**Table 1**)

Table 1. Baseline Characteristics

	30 mg (n=7)	150 mg (n=7)	450 mg (n=7)	900 mg (n=7)	Total participants (N=28)
Median (range) age, years	35 (18–55)	38 (27–61)	28 (25–62)	31 (24–43)	33 (18–62)
Female sex at birth, n (%)	1 (14.3)	1 (14.3)	1 (14.3)	0	3 (10.7)
Race, n (%)					
American Indian/Alaska Native	1 (14.3)	1 (14.3)	0	0	2 (7.1)
Asian	0	0	0	2 (28.6)	2 (7.1)
Black	3 (42.9)	3 (42.9)	0	0	6 (21.4)
Native Hawaiian/Pacific Islander	0	0	2 (28.6)	0	2 (7.1)
White	1 (14.3)	3 (42.9)	3 (42.9)	2 (28.6)	9 (32.1)
Other	2 (28.6)	0	2 (28.6)	3 (42.9)	7 (25.0)
Ethnicity, n (%)					
Hispanic or Latinx	4 (57.1)	2 (28.6)	2 (28.6)	5 (71.4)	13 (46.4)
Median (Q1–Q3) HIV-1 RNA, log_{10} copies/mL	4.36 (4.08–5.19)	4.74 (4.55–4.98)	5.31 (5.12–5.42)	4.90 (4.51–5.29)	4.90 (4.48–5.30)
Median (Q1–Q3) CD4+ T-cells/µL	454 (334–505)	264 (194–389)	350 (336–430)	440 (276–475)	370 (275–450)
ART naïve, n (%)	6 (85.7)	4 (57.1)	6 (85.7)	6 (85.7)	22 (78.6)

ART, antiretroviral therapy; Q, quartile.

Viral Load Decline

- One participant in the lowest dose cohort had virologic rebound during the monotherapy period
  - Maximum HIV-1 RNA reduction was –1.11 log_{10} copies/mL at D7, increasing to –0.26 log_{10} copies/mL at D11, with resuppression to <50 copies/mL on B/F/TAF
  - No INSTI resistance associated mutations (RAMs) or phenotypic changes to licensed INSTIs were detected at D11
- By D60, 24/27 participants had HIV-1 RNA <50 copies/mL
  - The three participants who did not reach HIV-1 RNA <50 copies/mL included one participant in the GS-1720 150 mg cohort and two participants in the GS-1720 450 mg cohort
  - All participants had considerable viral load decrease from baseline

Resistance Analysis

- All participants were phenotypically susceptible to GS-1720 and INSTIs at baseline
  - No primary INSTI RAMs were observed (**Table 2**)
  - Secondary INSTI RAMs were detected, with no impact on phenotypic sensitivity (**Table 3**)
- No treatment-emergent resistance to the INSTI class was detected at D11 or in those with SVR (**Tables 2 and 3**)
  - Phenotyping results for all participants at D11 demonstrated sustained susceptibility after monotherapy dosing relative to the wild-type for bictegravir, dolutegravir, elvitegravir, raltegravir, and GS-1720
- No treatment-emergent primary RAMs to the INSTI class were detected at D11 or follow-up (**Table 2**)
- No treatment-emergent secondary mutations to the INSTI class were detected at D11 or follow-up (**Table 3**)

Table 2. Participants With Primary INSTI RAMs

GS-1720 dose	Participants with Primary INSTI RAMs			
	Baseline	D11[a]	Follow-up in Participants with SVR[b]	Treatment-Emergent Resistance
30 mg (n=7)	0	0	-	0
150 mg (n=7)	0	0	0	0
450 mg (n=7)	0	0	0	0
900 mg (n=7)	0	0	-	0

[a]D11 samples were analysed for 27 participants. Genotypic data were obtained from 20/27 participants (74%) and phenotypic data were obtained from 12/27 participants (44%). [b]Two participants in the 150 mg group and two participants in the 450 mg group qualified for further INSTI genotypic and phenotypic resistance testing.
D, day; INSTI, integrase strand transfer inhibitor resistance; RAM, resistance-associated mutation; SVR, suboptimal virologic response.

Table 3. Participants With Secondary INSTI RAMs

GS-1720 dose	Participants with Secondary INSTI RAMs (n)			
	Baseline	D11[a]	Follow-up in Participants with SVR[b]	Treatment-Emergent Resistance
30 mg (n=7)	M50I (1) S119P/R/T (3) V151A/I/L (1) E157K/Q (1)	M50I (1) S119P/R/T (1) V151A/I/L (1) E157K/Q (1)	-	0
150 mg (n=7)	0	0	0	0
450 mg (n=7)	M50I (3) S119P/R/T (2)	M50I (3) S119P/R/T (2)	M50I (1) S119P/R/T (1)	0
900 mg (n=7)	M50I (2) S119P/R/T(2)	M50I (1) S119P/R/T (1)	-	0

[a]D11 samples were analysed for 27 participants. Genotypic data were obtained from 20/27 participants (74%) and phenotypic data were obtained from 12/27 participants (44%). [b]Two participants in the 150 mg group and two participants in the 450 mg group qualified for further INSTI genotypic and phenotypic resistance testing.
D, day; INSTI, integrase strand transfer inhibitor resistance; RAM, resistance associated mutation; SVR, suboptimal virologic response.

PK/PD Analysis

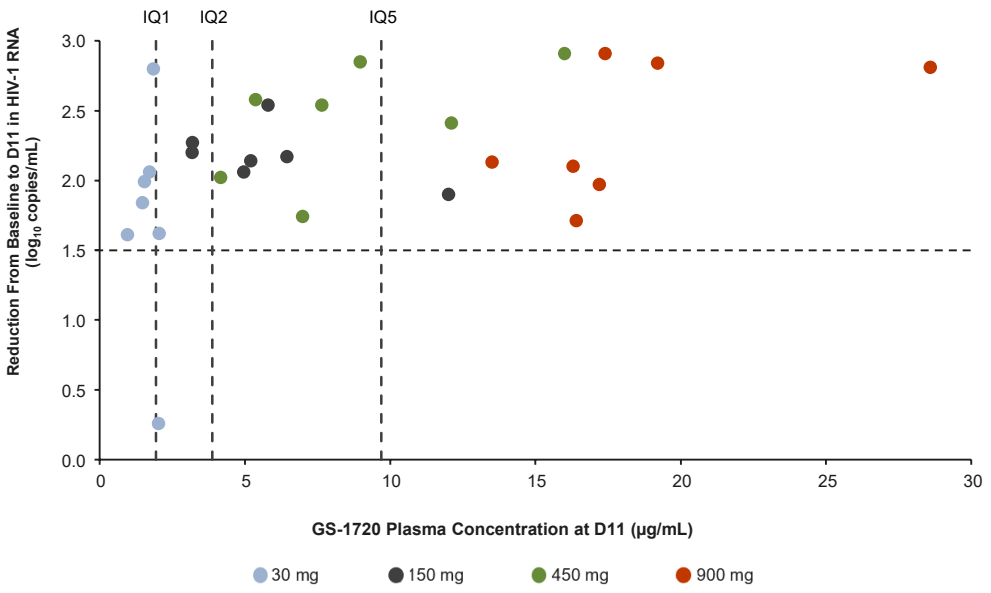
- Mean GS-1720 concentrations at D11 and HIV-1 RNA reductions from baseline to D11 are displayed in **Table 4**
- At D11, participants with GS-1720 concentrations above two-fold the IQ (IQ2; 3.876 µg/mL) showed robust antiviral activity of ≥1.5 log_{10} copies/mL reduction in HIV-1 RNA from baseline (**Figure 2**)

Table 4. Mean GS-1720 Concentrations and HIV-1 RNA Reductions From Baseline at D11

GS-1720 dose	Mean GS-1720 Concentrations at D11 (µg/mL)	Relative Mean IQ Values at D11 (µg/mL)	Mean Reduction From Baseline in HIV-1 RNA at D11 (log_{10} copies/mL)
30 mg (n=7)	1.64	0.8	1.74
150 mg (n=7)	5.87	3.0	2.18
450 mg (n=7)	8.78	4.5	2.44
900 mg (n=7)	18.4	9.5	2.37

D, day; IQ, inhibitory quotient.

Figure 2. PK/PD Analysis of GS-1720 at D11



Horizontal dashed line shows 1.5 log_{10} copies/mL reduction in HIV-1 RNA from baseline to D11. IQ is defined as protein-adjusted effective concentration to achieve 95% effective inhibition. IQ1 = 1.938 µg/mL; IQ2 = 3.876 µg/mL; IQ5 = 9.690 µg/mL.
D, day; IQ, inhibitory quotient; PD, pharmacodynamic; PK, pharmacokinetic.

Footnotes [a]Results from the GS-4182 Phase 1a study are presented in the HIV Glasgow 2024 poster #P036 (accessible via QR code)[5]. [b]NCT06544733 includes virologically suppressed PWH; NCT06613685 includes treatment-naïve PWH. [c]NCT05585307. [d]GeneSeq® Integrase sequences the IN gene to identify known RAM to the INSTI class. [e]PhenoSense® Integrase determines the phenotypic sensitivity to all currently approved antiretroviral drugs in the INSTI class (bictegravir, dolutegravir, elvitegravir, and raltegravir) and GS-1720. [f]Monogram Biosciences; South San Francisco, California, USA.

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Author Disclosures: **Brie Falkard, Haeyoung Zhang, Mutaz Jaber, Eva Mortensen, Furong Wang, Christian Callebaut,** and **Dhananjay D. Marathe** are all employees and shareholders of Gilead Sciences, Inc.

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