Phase 1a Safety and Pharmacokinetics of Single Ascending Doses of Oral GS-1720 in People Without HIV-1

WEPEB116

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Supplementary Figure QR Code

Conclusions

- GS-1720 exhibited less than dose-proportional pharmacokinetics (PK) with a median half-life of 9.3 days, which is suitable for once-weekly oral dosing
- GS-1720 had a favorable safety profile and was well tolerated at doses up to 1350 mg across the single ascending dose (SAD) cohorts
- Phase 1a SAD PK data were leveraged in a population pharmacokinetic (PopPK) model to inform dosing for a Phase 1b proof-of-concept study in people with HIV-1[1]
  - The PopPK model projections aligned with the observed data from the Phase 1b study
- These data support further clinical development of GS-1720 as part of an integrase strand transfer inhibitor (INSTI)-containing weekly oral antiretroviral (ARV) regimen

Plain Language Summary

- GS-1720 is a new long-acting medicine being developed to treat HIV infection, allowing dosing once per week instead of once per day
- GS-1720 is not yet approved for people to take outside of a clinical trial
- In this study, we tested single doses of GS-1720 in people who do not have HIV to see how the body processes this medicine and if it is safe
- We found that a single dose of GS-1720 caused only mild-to-moderate side effects and that GS-1720 is a good fit to take once a week
- Based on the results of this study, we are doing more studies to test whether GS-1720 is safe and works to treat HIV infection

Background

- Once-daily oral combination regimens are standard-of-care for treatment of HIV-1 infection[2]
- Lifelong adherence to antiretroviral therapies (ARTs) to reduce the risk of virologic failure is challenging for many people with HIV[3]
  - Novel long-acting oral ARTs remain an unmet need[4]
- GS-1720, a novel oral long-acting INSTI, has shown potent anti-HIV-1 activity in a Phase 1b study and could help address this unmet need[1]
  - In-vitro assessments showed protein-binding-adjusted 95% effective concentration value of 1.938 µg/mL (inhibitory quotient, IQ=1)
  - Nonclinical pharmacology profile of GS-1720 is detailed in poster #THPEA025[5]

Objective

- The safety, tolerability, and PK of escalating single and multiple doses of oral GS-1720 were evaluated in people without HIV-1 in this Phase 1a study
- Here, we present the PK and safety in the SAD cohorts
  - The multiple ascending dose (MAD) cohort data from this Phase 1a study will be presented in a future conference

Methods

- In this blinded, placebo-controlled study, 40 adults without HIV-1 were randomly assigned to GS-1720 (50, 150, 450, or 1350 mg with n=8 per cohort) or placebo (n=2 per cohort) under fasting conditions, and all participants were followed until Day 70
- Primary endpoints were plasma PK parameters including maximum concentration (C_{max}), area under the concentration-versus-time curve extrapolated-to-infinity (AUC_{inf}), time taken to reach the maximum concentration (T_{max}), % area under the curve (AUC) extrapolated at AUC_{inf}, terminal half-life ($t_{1/2}$); incidence of adverse events (AEs) and laboratory abnormalities
- A validated high-performance liquid chromatography with tandem mass spectrometry method was developed and used to quantify plasma concentrations of GS-1720; PK parameters were estimated using Phoenix WinNonlin® software noncompartmental methods
- PopPK modeling was developed using preliminary SAD PK data
  - A two-compartment PopPK model with dose-dependent saturation of absorption was used (**Figure 2**); allometric scaling by body weight was used for clearance and volume parameters
  - Model-simulated GS-1720 concentrations for Day 11 were used to inform on Phase 1b dosing (30, 150, 450, and 900 mg on Day 1 and Day 2)

Results

Participant details

- Baseline characteristics were generally balanced between the four cohorts (**Table 1**)
  - Median age was 33 years, and 50% of participants were male

Table 1. Baseline Characteristics

	50 mg (n=8)	150 mg (n=8)	450 mg (n=8)	1350 mg (n=8)	Pooled Placebo (n=8)
Median (Q1–Q3) age, years	36 (28–42)	35 (29–42)	33 (25–37)	30 (25–35)	36 (29–41)
Male, n (%)	5 (62.5)	3 (37.5)	3 (37.5)	5 (62.5)	4 (50.0)
Race, n (%)					
White	6 (75.0)	5 (62.5)	5 (62.5)	5 (62.5)	7 (87.5)
Black	2 (25.0)	2 (25.0)	2 (25.0)	0	1 (12.5)
Asian	0	0	1 (12.5)	2 (25.0)	0
American Indian or Alaska Native	0	1 (12.5)	0	0	0
Other	0	0	0	1 (12.5)	0
Ethnicity, n (%)					
Hispanic or Latinx	3 (37.5)	3 (37.5)	2 (25.0)	5 (62.5)	4 (50.0)
Mean (SD) BMI, kg/m²	27.6 (3.1)	27.9 (2.36)	24.8 (4.31)	27.5 (2.64)	25.3 (3.30)

BMI, body mass index; Q, quartile; SD, standard deviation.

Pharmacokinetic data

- Across the four SAD cohorts, GS-1720 demonstrated nonlinear PK, resulting in less-than-dose proportional increases in exposure (C_{max}, AUC_{inf}) with increasing dose (**Figure 1, Table 2**)
  - With each three-fold dose increase in GS-1720, C_{max} and AUC_{inf} increases ranged from 1.6- to 2.2-fold and 1.8- to 2.5-fold, respectively
  - Across a 27-fold dose increase, 6.51-fold and 8.55-fold C_{max} and AUC_{inf} increases were observed, respectively
- GS-1720 median T_{max} was 4 hours, and $t_{1/2}$ was 9.3 days (**Table 2**)

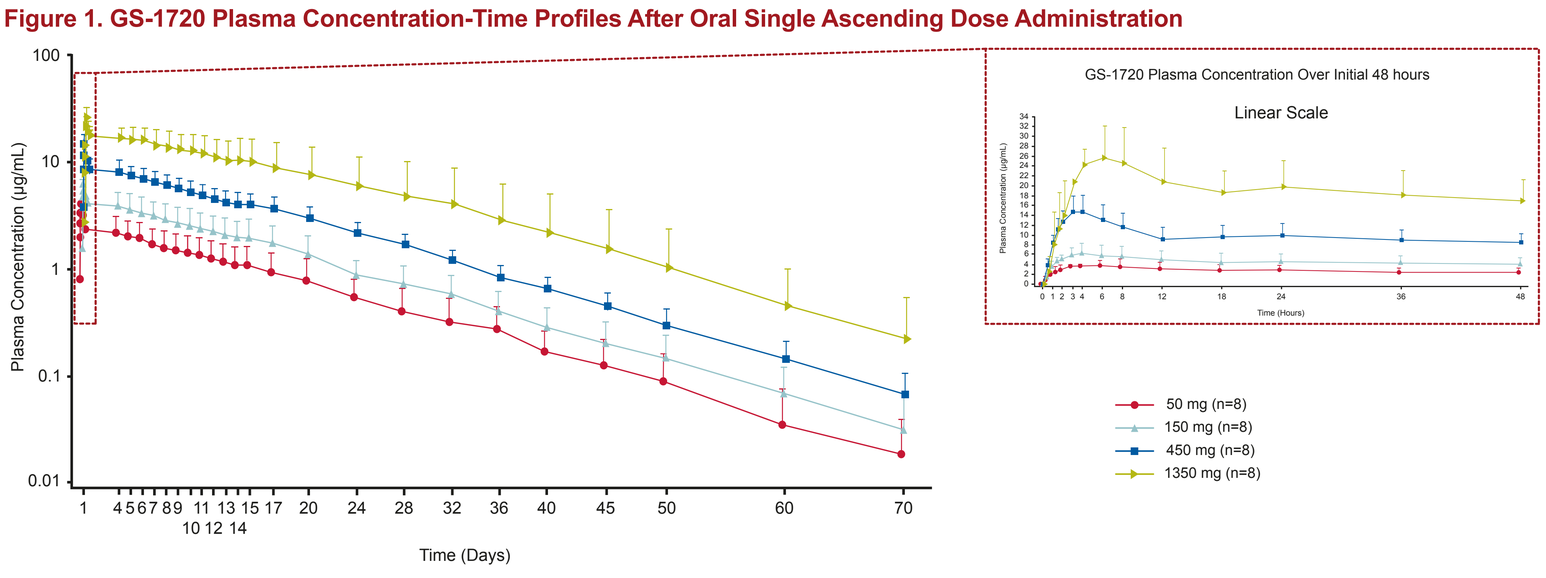
Table 2. GS-1720 PK Parameters After Oral Single Ascending Dose Administration

GS-1720 PK Parameters	50 mg (n=8)	150 mg (n=8)	450 mg (n=8)	1350 mg (n=8)
Mean C_{max} (%CV), µg/mL GLSM ratio versus 50 mg, % (90% CI)	4.30 (28.3) -	6.86 (28.1) 158 (128; 195)	15.0 (21.5) 349 (284; 430)	27.7 (20.8) 651 (529; 802)
Mean AUC_{inf} (%CV), hr*µg/mL GLSM ratio versus 50 mg, % (90% CI)	944 (46.5) -	1660 (41.1) 174 (125; 243)	3440 (22.0) 380 (272; 531)	8500 (59.8) 855 (613; 1190)
Median T_{max} (Q1–Q3), hours	3.5 (2.5–5.0)	4.0 (2.5–5.04)	4.0 (3–4)	5.0 (3.5–6.0)
Mean % AUC_{exp} (%CV), %	0.778 (28.0)	0.690 (52.3)	4.02 (234)	0.723 (83.8)
Median $t_{1/2}$ (Q1–Q3), days	9.5 (7.8–11.2)	9.0 (8.1–11.3)	9.7 (7.0–11.4)	9.4 (7.7–12)

Please note that placebo data are not shown.
AUC_{exp}, percentage of AUC extrapolated between AUC_{last} and AUC_{inf}; AUC_{inf}, AUC_{inf}; C_{max}, maximum concentration; CI, confidence interval; CV, coefficient of variation; GLSM, geometric least-squares mean; PK, pharmacokinetics; Q, quartile; T_{max}, time taken to reach the maximum concentration; $t_{1/2}$, half-life.

Results (cont.)

Figure 1. GS-1720 Plasma Concentration-Time Profiles After Oral Single Ascending Dose Administration



Graph shows a semi-log scale of mean (+SD) GS-1720 plasma concentrations.

Safety

- GS-1720 was generally well tolerated, with a favorable safety profile (**Table 3**)
  - No dose-related effects on the incidence or nature of AEs were observed across the SAD cohorts
- No serious AEs, Grade 3/4 AEs, AEs leading to study drug discontinuation, or clinically significant laboratory abnormalities at any dose level were observed

Table 3. GS-1720 Safety Profile After Oral Single Ascending Dose Administration

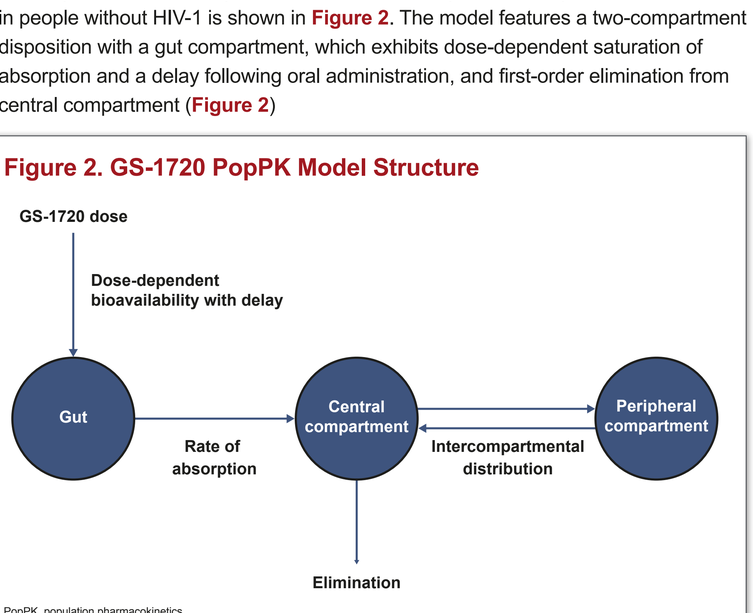
	50 mg (n=8)	150 mg (n=8)	450 mg (n=8)	1350 mg (n=8)	Pooled Placebo (n=8)
Any Grade TEAE	1 (12.5)	5 (62.5)	4 (50.0)	5 (62.5)	2 (25.0)
Any Grade ≥3 TEAE	0	0	0	0	0
Any TE SAE	0	0	0	0	0
Any study drug-related TEAE[a]	0	0	2 (25.0)	2 (25.0)	0
Any Grade ≥3 study drug-related TEAE	0	0	0	0	0
Any study drug-related TE SAE	0	0	0	0	0
Any TEAE leading to premature discontinuation of study drug	0	0	0	0	0
Any Grade 3 laboratory abnormalities	0	2 (25.0)	1 (12.5)	0	1 (12.5)

[a]Study drug-related TEAEs in the 450 mg and 1350 mg cohorts were headache, fatigue, vertigo, and elevated creatine kinase.
SAE, serious adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event.

GS-1720 PopPK Model Development

- The PopPK model developed to describe the absorption and disposition of GS-1720 in people without HIV-1 is shown in **Figure 2**. The model features a two-compartment disposition with a gut compartment, which exhibits dose-dependent saturation of absorption and a delay following oral administration, and first-order elimination from central compartment (**Figure 2**)

Figure 2. GS-1720 PopPK Model Structure

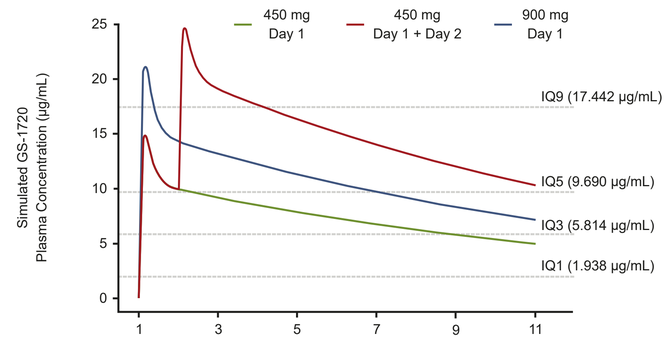


PopPK, population pharmacokinetics.

- The established model was able to describe the observed GS-1720 concentrations in Phase 1a SAD cohorts (**Supplementary Figure**; see QR code at top right)
  - The model-derived $t_{1/2}$ was consistent with observed half-life $t_{1/2}$ (approximately 9 days)
- The model informed on:
  - Frequency of dosing: Day 1 + Day 2 dosing was preferable over Day 1-only dosing (**Figure 3**)
  - Dose levels for the Phase 1b study targeting a range of concentrations at Day 11 (**Figure 4**)
- PopPK model performance showed alignment with Ph1b observed concentrations at Day 11 (**Figure 5**)

Figure 3. PopPK Model Simulations to Support Day 1 + Day 2 Dosing

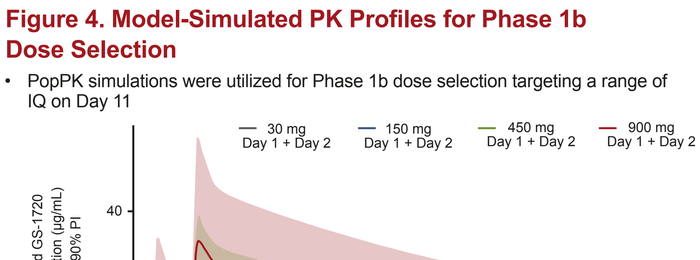
- Frequency evaluation: simulated GS-1720 concentration (µg/mL) up to Day 11 after receiving 450 mg on Day 1, 450 mg on Days 1 and 2, or 900 mg on Day 1
- Day 1 + Day 2 dosing was projected to achieve higher trough exposures at Day 11 (Phase 1b primary endpoint) than the same cumulative dose (900 mg) administered on Day 1 alone



GS-1720 simulated projections shown are based on average PopPK parameters (typical individual with 70 kg body weight).
IQ, inhibitory quotient; PK, pharmacokinetics; PopPK, population PK.

Figure 4. Model-Simulated PK Profiles for Phase 1b Dose Selection

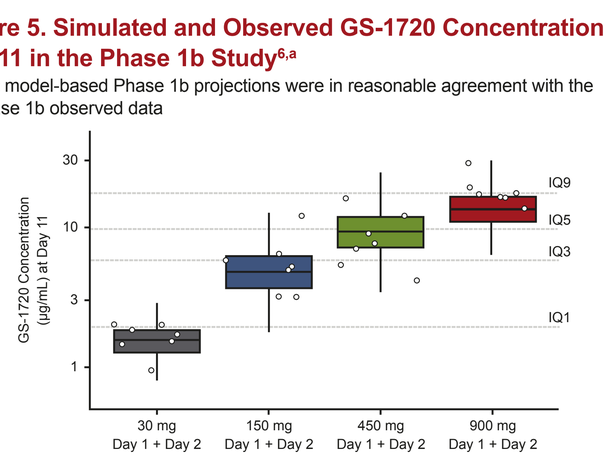
- PopPK simulations were utilized for Phase 1b dose selection targeting a range of IQ on Day 11



Simulation was conducted using 1000 (variability terms) in-silico patients for each dose level.
IQ, inhibitory quotient; PI, prediction interval; PopPK, population pharmacokinetics.

Figure 5. Simulated and Observed GS-1720 Concentration at Day 11 in the Phase 1b Study[6,a]

- The model-based Phase 1b projections were in reasonable agreement with the Phase 1b observed data



- Boxplot shows the simulated 25th, 50th (median) and 75th percentiles based on the lower, middle and upper box hinges, respectively
  - The upper and lower whiskers extend to +/- 1.5 times the interquartile range, respectively
- Observed concentrations at Day 11 in the Phase 1b study are presented as jittered white dots and are stratified by Phase 1b doses

[a]NCT05585307, Substudy-02 (GS-US-544-5905-02). Simulated GS-1720 concentrations are shown on a semi-log scale.
Number of participants for each cohort is 7.Simulation was conducted by replicating Phase 1b dosing 1000 times using participants demographics.
IQ1 (1.938 µg/mL), IQ3 (5.814 µg/mL), IQ5 (9.690 µg/mL), and IQ9 (17.442 µg/mL) are concentrations related to the activity of GS-1720.
IQ, inhibitory quotient.

References: **1.** Fichtenbaum CJ, et al. CROI, Denver, Colorado, March 3–6, 2024. **2**. Zhao AV, et al. *Retrovirology*. 2022;19:22 **3**. Scarsi KK, et al. *J Int Assoc Provid AIDS Care*. 2021 Jan–Dec;20:23259582211009011. **4**. Enriquez M, McKinsey DS. *HIV AIDS - Research and Palliative Care*. 2011;3:45–51. **5**. Hansen D, et al. AIDS, Munich, Germany, July 22–26, 2024. **6**. Study of Novel Antiretrovirals in Participants With HIV-1. Available from: https://clinicaltrials.gov/study/NCT05585307 (Accessed June 2024).

Disclosures: **Haeyoung Zhang, Mutaz Jaber, Eva Mortensen, Hui Wang, Ines Mendes, Monika Sobczyk, Aaron Share, Ramesh Palaparthy**, and **Dhananjay D Marathe** are all employees and shareholders of Gilead Sciences, Inc.

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