Antiviral Activity, Safety, and Pharmacokinetics of GS-1720, a Novel Weekly Oral INSTI

Carl J. Fichtenbaum*[1], Mezgebe Berhe[2], Jose Bordon[3], Jacob Lalezari[4], Godson Oguchi[5], Gary Sinclair[6], Furong Wang[7], Brie Falkard[7], Haeyoung Zhang[7], Ana Z. Gonzalez[7], Eva Mortensen[7], Jared Baeten[7], Moti Ramgopal[8]

[1]University of Cincinnati, Cincinnati, OH, USA; [2]North Texas Infectious Diseases Consultants, Dallas, TX, USA; [3]Washington Health Institute, Washington, DC, USA; [4]Quest Clinical Research, San Francisco, CA, USA; [5]Midland Florida Infectious Diseases Specialists, Orange City, FL, USA; [6]Prism Health North Texas, Dallas, TX, USA; [7]Gilead Sciences, Foster City, CA, USA; [8]Midway Immunology and Research Center, Fort Pierce, FL, USA

*Presenting author

CROI, March 3–6 2024, Denver, Colorado, USA. Oral: 1903

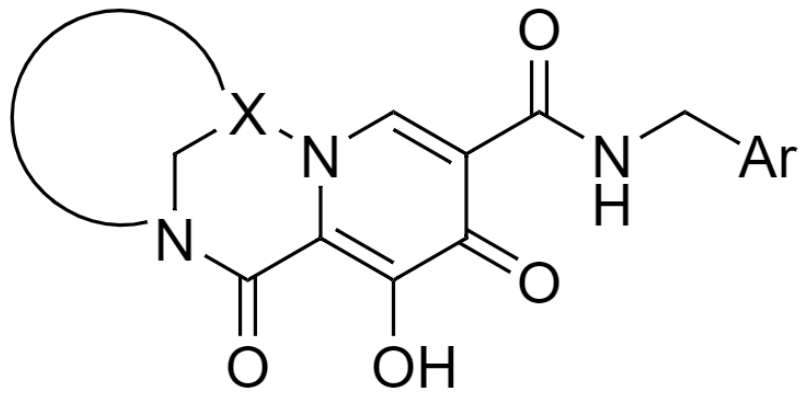
Disclosures

- Carl J. Fichtenbaum reports research study support to institution from Gilead Sciences, Inc., Merck, ViiV, and Moderna, and advisory board membership in the past 12 months for ViiV Healthcare, and Theratechnologies
- Mezgebe Berhe, Jose Bordon, Jacob Lalezari, and Godson Oguchi declare no competing interests
- Gary Sinclair reports research study support from Gilead Sciences, Inc., ViiV, Merck, AbbVie, Janssen ID/Vaccines, and Theratechnologies, and honoraria from ViiV, Merck, Janssen ID/Vaccines, and Theratechnologies
- Furong Wang, Brie Falkard, Haeyoung Zhang, Ana Z. Gonzalez, Eva Mortensen, and Jared Baeten are all employees and shareholders of Gilead Sciences, Inc.
- Moti Ramgopal reports consulting fees from Gilead Sciences, Inc., ViiV, and Merck, plus honoraria from Gilead Sciences, Inc., ViiV, and AbbVie

Background

- Once-daily oral combination regimens containing integrase strand transfer inhibitors (INSTIs) are standard of care for treatment of HIV-1 infection[1]
- Oral long-acting antiretroviral therapies (ARTs) remain an unmet need and could increase adherence and satisfaction[2]
- GS-1720 is a potent, orally bioavailable INSTI, with picomolar antiviral activity and a pharmacokinetic profile well suited for once-weekly oral dosing

GS-1720



We conducted two studies to assess the pharmacokinetics, safety, and antiviral activity of GS-1720: a Phase 1a study in adults without HIV-1 and a Phase 1b study in adults with HIV-1

1. Zhao AV, et al. *Retrovirology*. 2022;19:22; 2. Enriquez M and McKinsey DS. *HIV/AIDS - Res. Palliat. Care*. 2011;3:45–51.

Phase 1a: GS-1720 Half-Life Shows Potential for Once-Weekly Dosing

Objective: To evaluate the safety, tolerability, and pharmacokinetics of escalating single and multiple doses of oral GS-1720

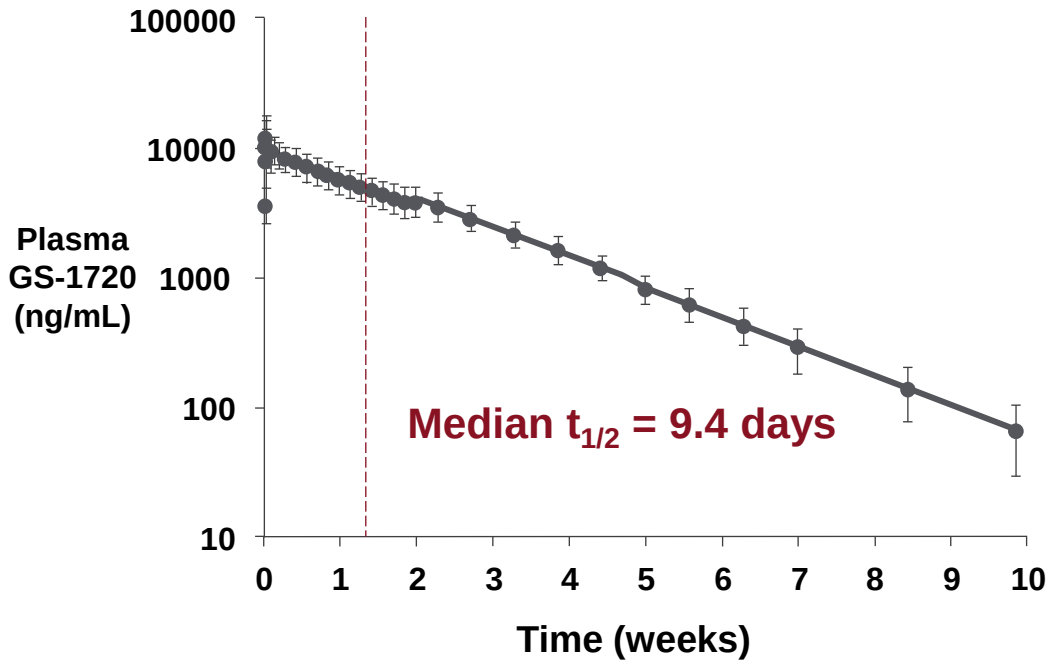
Adults without HIV-1 aged 18–45 years

4 single-dose cohorts[a]
50 to ≤1350 mg vs placebo

3 multiple-dose cohorts[a]
up to 1350 mg vs placebo

Other cohorts[b]

GS-1720 concentration-time profile following a single 450 mg dose[c,d]



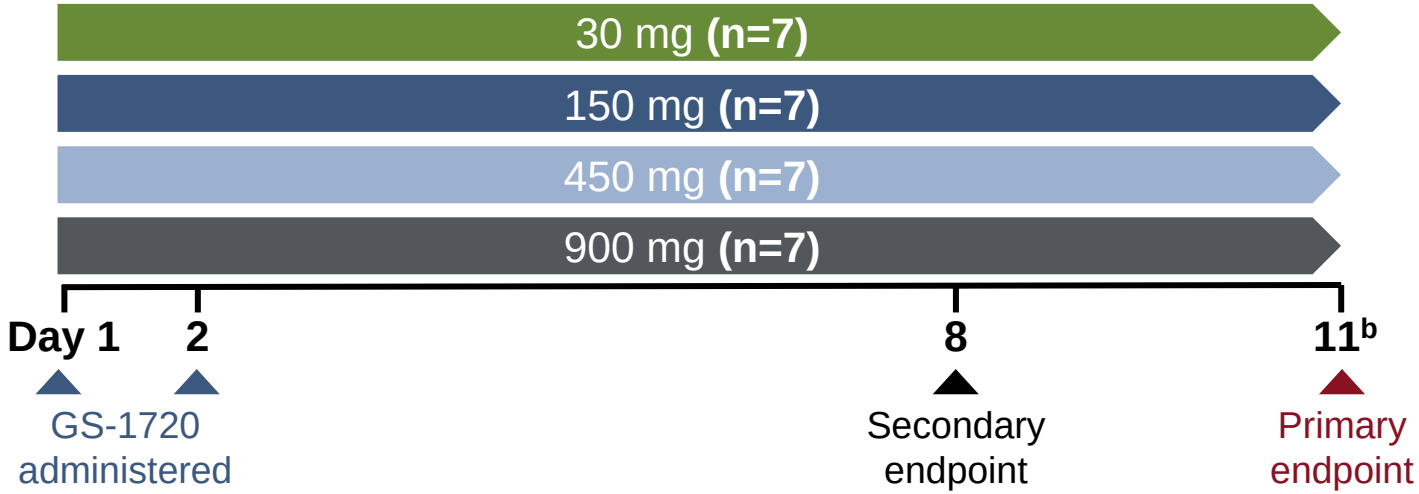
[a]Single/multiple dose cohorts were randomized, blinded, and placebo-controlled, with adaptive GS-1720 dose selection. [b]Other cohorts included food effect and drug-drug interaction cohorts. [c]GS-1720 (n=8) and matched placebo (n=2) was administered under fasting conditions as a single 450 mg oral dose. [d]Data from Phase 1a study of GS-1720 will be presented in detail at future congresses.
$t_{1/2}$, half-life

Phase 1b Study in Adults With HIV-1: Study Design[a]

Objective: To investigate the antiviral activity, safety, and pharmacokinetics of GS-1720

Key inclusion criteria:

- HIV-1 RNA 5000 to ≤400,000 copies/mL
- CD4+ T-cells >200 cells/μL
- Treatment-naïve *OR* treatment-experienced and naïve to INSTIs and off ART for >12 weeks



Primary endpoint:

- Plasma HIV-1 RNA (log_{10} copies/mL) change from baseline to Day 11 relative to historical placebo

Secondary endpoints included:

- Safety and tolerability
- Resistance to INSTIs at Baseline and Day 11

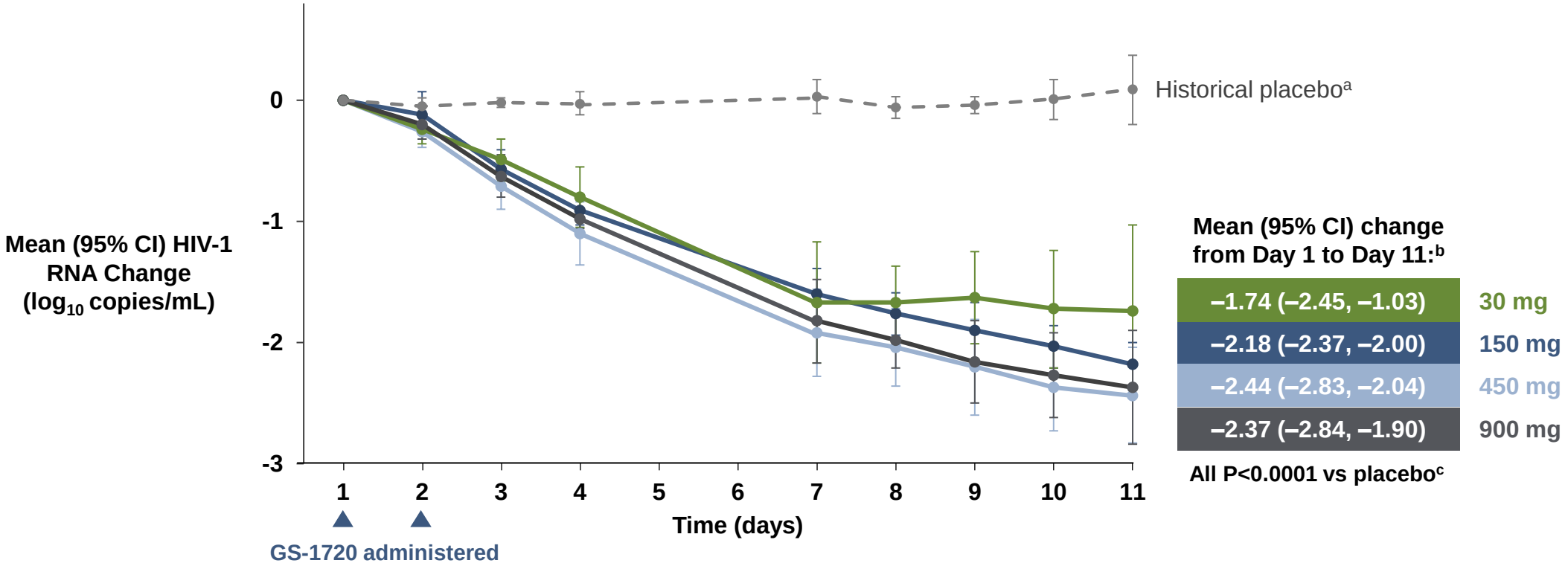
[a]NCT05585307, Substudy-02. [b]After Day 11, participants initiated an alternative standard-of-care ART regimen, selected by the investigator.
ART, antiretroviral therapy; **INSTI,** integrase strand transfer inhibitor
clinicaltrials.gov/ct2/show/NCT05585307.

Phase 1b: Baseline Characteristics

	Total participants[a] (N=28)
Median (range) age, years	33 (18–62)
Female, n (%)	3 (10.7)
Race, n (%)	
American Indian/Alaska Native	2 (7.1)
Asian	2 (7.1)
Black	6 (21.4)
Native Hawaiian/Pacific Islander	2 (7.1)
White	9 (32.1)
Other	7 (25.0)
Ethnicity, n (%)	
Hispanic or Latinx	13 (46.4)
Median (Q1–Q3) HIV-1 RNA, $\log_{10}$ copies/mL	4.90 (4.48–5.30)
Median (Q1–Q3) CD4+ T-cells/µL	370 (275–450)
ART-naïve, n (%)	23 (82.1)
Participants with INSTI resistance, n (%)	0

[a]Total of 4 cohorts, n=7 in each cohort
ART, antiretroviral therapy; **INSTI,** integrase strand transfer inhibitor; **Q**, quartile

Phase 1b: GS-1720 Exhibited Potent Antiviral Activity

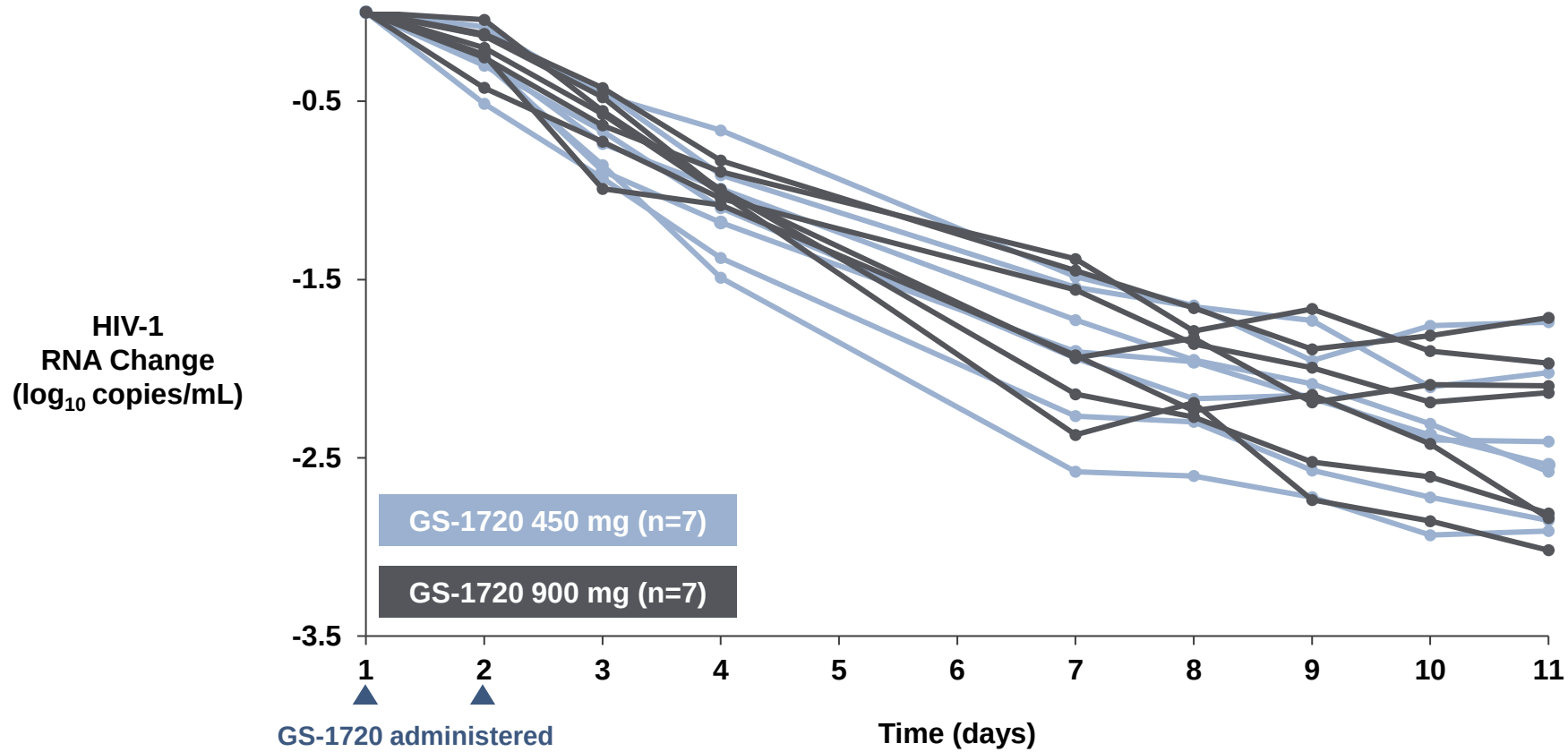


- No treatment-emergent INSTI resistance was observed at Day 11 in the 150 mg and 450 mg cohorts[d]
  - Resistance testing for the 30 mg and 900 mg cohorts is currently ongoing

Reference – Bictegravir at 50 and 100 mg once daily (target therapeutic range): ΔVL_{10}= 2.08 and 2.43[1]. [a]Historical placebo (HIV-1 RNA change from Day 1 = +0.01 log_{10} copies/mL) includes placebo-treated participants from three previous Gilead-sponsored studies; for historical studies without Day 11 HIV-1 RNA, Day 10 values were used for Day 11. [b]n=7 per cohort. [c]Pairwise P-value vs placebo. [d]All participants in the 150 mg and 450 mg cohorts were tested for resistance at Day 11. **CI,** confidence interval; **INSTI,** integrase strand transfer inhibitor; **VL**, viral load.

1. Gallant JE, et al. *J Acquir Immune Defic Syndr*. 2017;75(1):61–66.

Phase 1b: 450 and 900 mg Doses Showed Potent Antiviral Activity Across All Individuals



- Target therapeutic range resulted in robust antiviral activity in all participants

Phase 1b: Adverse Events and Laboratory Abnormalities

Participants with event, n (%)	30 mg (n=7)	150 mg (n=7)	450 mg (n=7)	900 mg (n=7)
Any Grade AE	**5 (71.4)**	**6 (85.7)**	**3 (42.9)**	**4 (57.1)**
Any Grade ≥3 AE[a]	0	2 (28.6)	0	0
Atrial fibrillation	0	1 (14.3)	0	0
Device loosening	0	1 (14.3)	0	0
Any SAE	0	1 (14.3)[b]	0	0
Any study drug-related AE	**2 (28.6)**	**1 (14.3)**	**0**	**1 (14.3)**
Any Grade ≥3 study drug-related AE	0	0	0	0
Any study drug-related SAE	0	0	0	0
Any AE leading to premature discontinuation of study drug	**0**	**0**	**0**	**0**
Any Grade 3 laboratory abnormalities[c]	**1 (14.3)**	**1 (14.3)**	**0**	**0**

[a]Grade 3 AEs included (n=1 each): atrial fibrillation (Day 11–13), device loosening (prosthetic left hip); both unrelated to study drug. [b]Atrial fibrillation, n=1. [c]No Grade 4 laboratory abnormalities; Grade 3 laboratory abnormalities included: increased creatinine and decreased CrCl (n=1; onset Day 25) in 150 mg cohort and decreased CrCl (n=1; onset Day 3, with Grade 2 at baseline) in 30 mg cohort.
AE, adverse event; **CrCl,** creatinine clearance; **SAE,** serious adverse event

Conclusions

- GS-1720 has a pharmacokinetic profile suitable for weekly dosing
- GS-1720 demonstrated potent antiviral activity with a mean >2 $\log_{10}$ copies/mL decline in HIV-1 RNA in the highest dose cohorts, comparable to currently approved once-daily INSTIs[1]
- No treatment-emergent INSTI resistance was observed at Day 11, with resistance testing for two cohorts ongoing
- GS-1720 was well tolerated with a favorable safety profile

These data support further clinical development of GS-1720 as part of the first INSTI-containing weekly oral single-tablet regimen

INSTI, integrase strand transfer inhibitor

1. Zhao AV, et al. *Retrovirology*. 2022;19:22.

Acknowledgements

- We extend our thanks to the participants, their families, and all participating investigators and staff
- This study was funded by Gilead Sciences, Inc.
- All authors contributed to and approved the presentation; medical writing support was provided by Sophie Roberts of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by Gilead Sciences, Inc.

- Correspondence: FICHTECJ@UCMAIL.UC.EDU