Safety, Pharmacokinetics, and Antiviral Activity of GS-3242, a Novel Long-Acting Injectable INSTI

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Disclosures

- Samir Gupta has received advisory fees from Gilead Sciences, Inc., ViiV Healthcare, and Infectious Diseases Society of America, and unrestricted research grant funding from ViiV Healthcare.
- Mezgebe Berhe reports nothing to disclose
- Roberto Ortiz reports nothing to disclose
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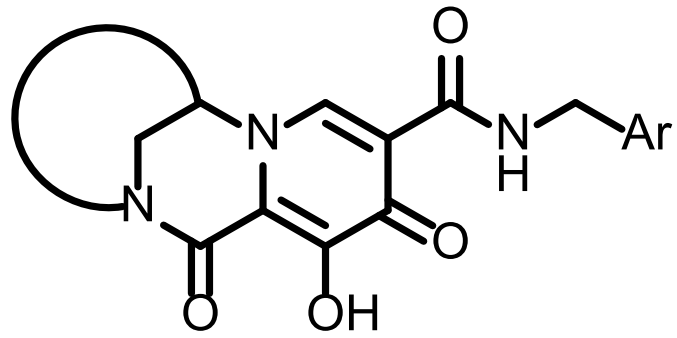
Background

- Regimens containing integrase strand transfer inhibitors (INSTIs) are the standard of care for treatment of HIV-1 infection[1]
- Long-acting antiretrovirals may help to address suboptimal adherence, stigma, and treatment fatigue associated with daily oral antiretroviral therapy[2]
- GS-3242 is a novel, investigational INSTI with potent pre-clinical anti-HIV-1 activity and physiochemical properties well-suited for a long-acting formulation[3,4]
  - See CROI 2026 Posters 521 and 490

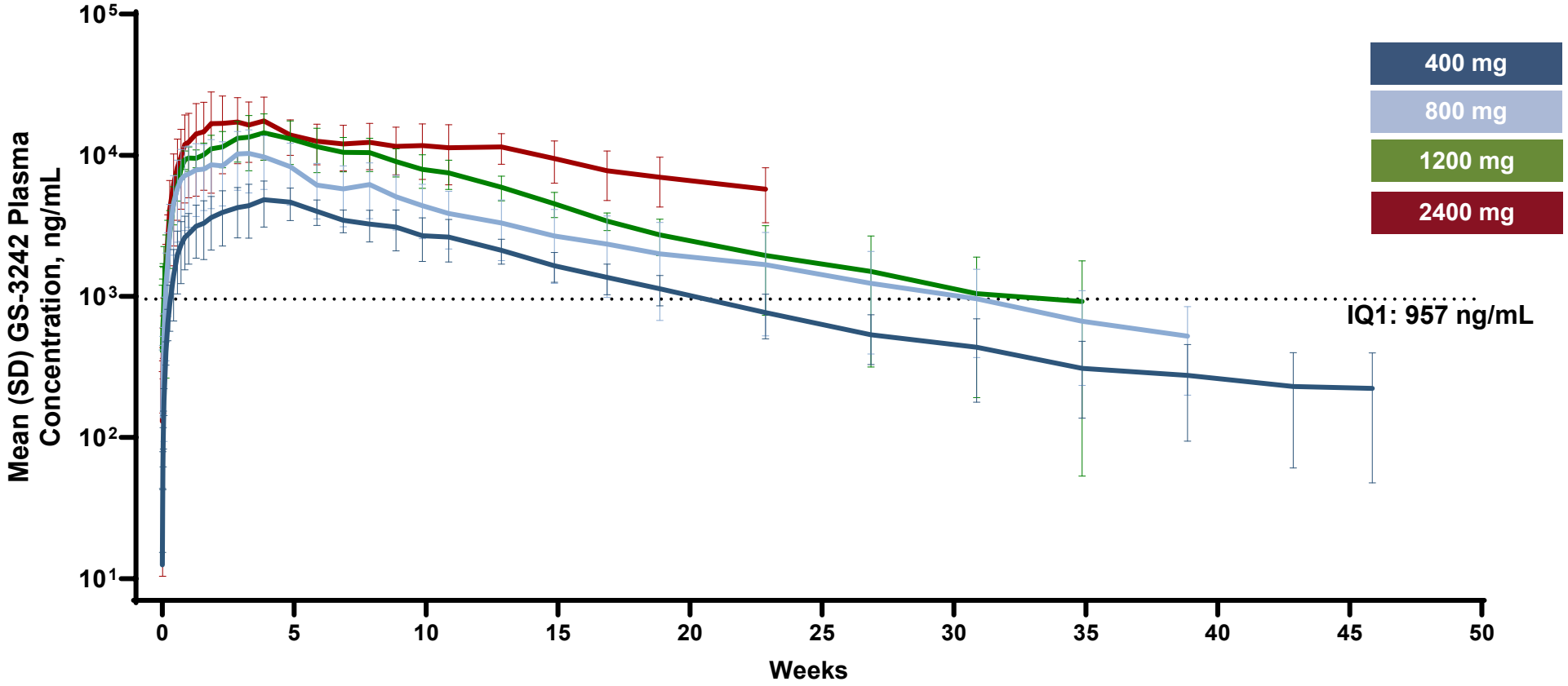
GS-3242



Here, we present results from an ongoing Phase 1a and a Phase 1b study evaluating the safety, pharmacokinetics (PK), and antiviral activity of GS-3242

1. Zhao AV, et al. *Retrovirology*. 2022;19:22; 2. Claborn KR, et al. *Psychol Health Med* 2015; 20(3):255-65. 3. Hansen D, et al. CROI 2026. Poster 521. 4. Subramanian M, et al. CROI 2026. Poster 490.

Phase 1a: GS-3242 Concentrations Following a Single Intramuscular (IM) Dose in People without HIV-1[a]



These PK data support a dosing interval of at least 4 months

[a]Administered in the thigh; cohorts were randomized, blinded, and placebo-controlled (3:1), with GS-3242 dose escalation (28 male; 7 female). Preliminary data, study is ongoing.
IQ1, inhibitory quotient 1, defined as the protein-adjusted 95% effective concentration (paEC95) value.

Phase 1a: GS-3242 Shows Potential for an Extended Dosing Interval

Intramuscular GS-3242 PK Parameters

Parameter[a]	400 mg (n=6)	800 mg (n=6)	1200 mg (n=5)	2400 mg (n=6)
T_{max} , days	34.1 (27–42)	21.5 (13–27)	27.0 (6–27)	27.0 (13–34.1)
C_{max} , ng/mL	5062 (31%)	9640 (52%)[b]	14,580 (36%)	19,323 (53%)
AUC_{inf} , µg*h/mL	11,564 (11%)	22,137 (30%)[b,c]	31,877 (11%)[c]	NC
$t_{1/2}$, day	76 (32–146)	63 (36–151)[b]	50 (19–87)	70 (33–333)

Additional cohorts to evaluate a 6-month dosing interval are underway

[a]Parameters are reported as mean (% coefficient of variation), except for T_{max} and $t_{1/2}$ which are reported as median (min–max). [b]n=5. [c]Preliminary data: with some participant data showing an $AUC_{extrap\%}$ higher than 20%, longer follow-up is needed. **AUC**, area under the concentration time curve; **AUC_{inf}**, AUC extrapolated to infinity; **$AUC_{extrap\%}$**, the portion of AUC_{inf} that was extrapolated; **C_{max}**, maximum concentration; **NC**, not calculated; **PK**, pharmacokinetics; **$t_{1/2}$**, half-life; **T_{max}**, time to C_{max}

Phase 1a: IM GS-3242 Shows Favorable Safety and Tolerability

Blinded Safety Data (IM GS-3242 or Placebo)

Participants n, (%)	400 mg or placebo (N=9)	800 mg or placebo (N=8)	1200 mg or placebo (N=9)	2400 mg or placebo (N=8)
Any AE	5 (55.6)	4 (50.0)	8 (88.9)	8 (100)
Grade ≥3	0	0	0	0
Treatment-related AEs	2 (22.2)	3 (37.5)	7 (77.8)	7 (87.5)
Grade ≥3	0	0	0	0
Any ISR	3 (33.3)	3 (37.5)	7 (77.8)	7 (87.5)
Grade 1 injection site pain	2 (22.2)	2 (25.0)	3 (33.3)	6 (75.0)
Grade 2 injection site pain	0	1 (12.5)	4 (44.4)	1 (12.5)
Grade 1 Injection site bruising	1 (11.1)	0	0	0
Serious AE	0	0	0	0
Grade ≥3 laboratory abnormalities[a]	1 (11.1)	1 (14.3)[b]	2 (22.2)	1 (12.5)

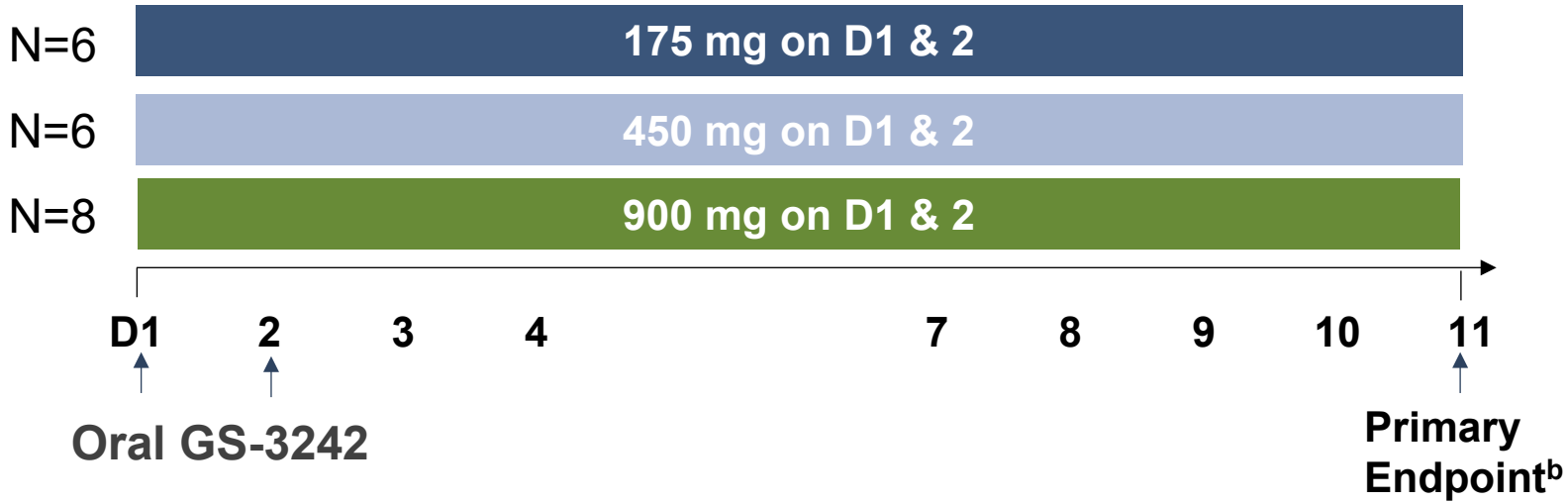
[a]Grade ≥3 laboratory abnormalities included high creatine kinase (n=1), low creatinine clearance (n=1), hypercholesterolemia (n=1), high LDL cholesterol (n=1), high bilirubin (n=1), and glycosuria (n=1).
[b]The post-baseline value was only available for 7 of 8 participants, which is reflected in the denominator.
AE, adverse event; **IM**, intramuscular; **ISR**, injection site reaction.

Open Label Phase 1b Study in Adults With HIV-1[a]

Objective: To investigate the antiviral activity, safety, and PK of oral GS-3242 in adults with HIV-1

Eligibility Criteria

- PWH ≥18 years
- Treatment naïve, or
- Naïve to long-acting injectable ART and the INSTI class
- Off ART/PrEP for ≥12 weeks
- HIV-1 RNA 5,000–400,000 copies/mL
- CD4+ T-cells >200 cells/µL



Primary endpoint:

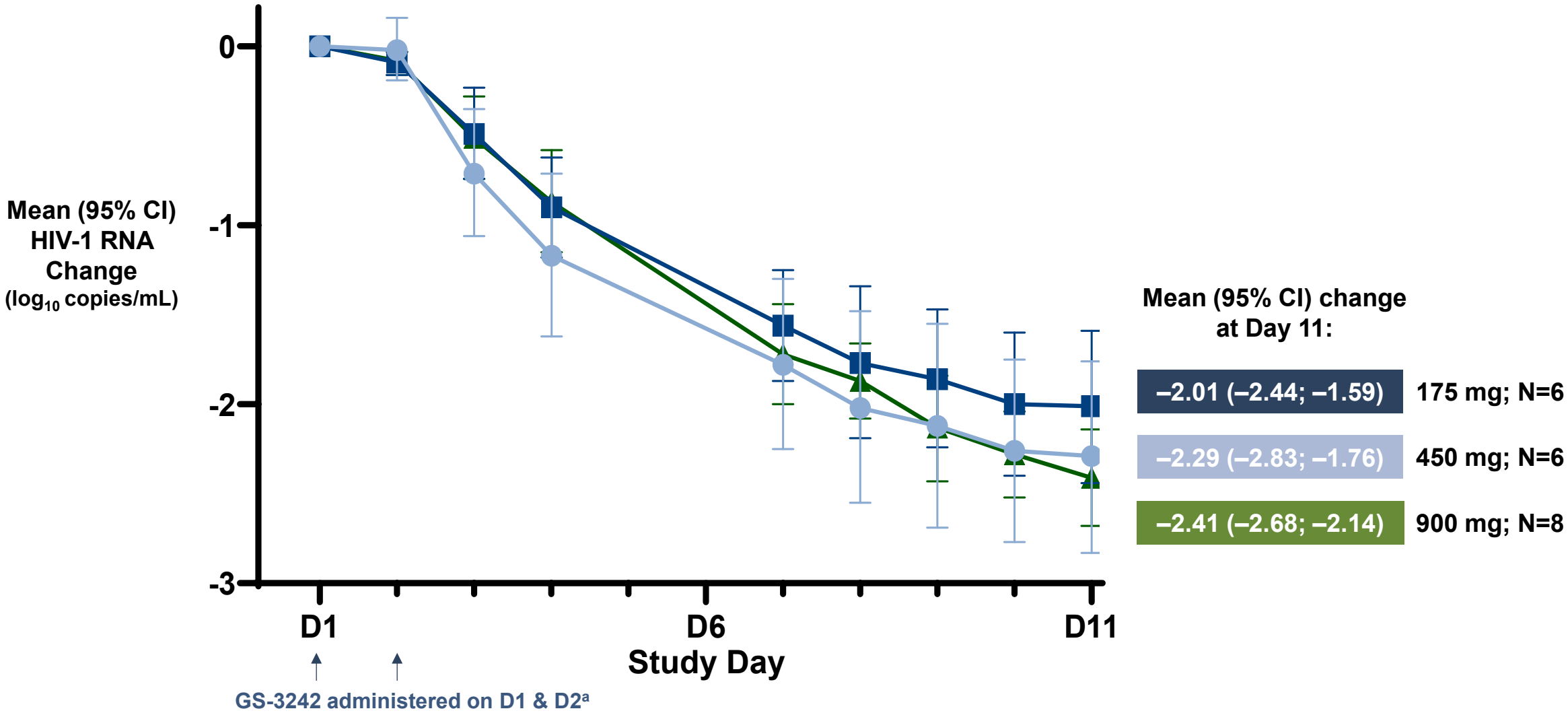
- Change in plasma HIV-1 RNA (log_{10} copies/mL) from baseline to Day 11

Secondary endpoints included:

- Safety and tolerability
- Resistance to INSTIs at Baseline and Day 11 (data pending)

[a]NCT07001319. [b]Participants initiated B/F/TAF or other SOC on D11.
ART, antiretroviral therapy; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **D**, day; **INSTI,** integrase strand transfer inhibitor; **PK**, pharmacokinetics; **PrEP**, pre-exposure prophylaxis; **PWH**, people with HIV-1; **SOC**, standard of care

Phase 1b: GS-3242 Shows Potent Antiviral Activity



[a]17 male; 3 female were enrolled and dosed.
D, day.

Phase 1b: Oral GS-3242 Shows Favorable Safety and Tolerability

Participants n, (%)	175 mg (N=6)	450 mg (N=6)	900 mg (N=8)
Any AE	2 (33.3)	2 (33.3)	1 (12.5)
Grade 2[a]	0	1 (16.7)	0
Treatment-related AEs	1 (16.7)	0	0
Serious AE	0	0	0
AE leading to discontinuation	0	0	0
Grade ≥3 laboratory abnormalities[b]	1 (16.7)	1 (16.7)	2 (25.0)

[a]There were no Grade ≥3 AEs. [b]Grade ≥3 laboratory abnormalities included creatine kinase increase (n=1), low creatinine clearance (n=1), increased creatinine (n=1), increased lipase (n=1), hyperglycemia (n=1), increased LDL (n=1).
AE, adverse event; **LDL**, low-density lipoprotein.

Conclusions

- GS-3242 was well tolerated and shows a favorable safety profile
- GS-3242 demonstrated potent antiviral activity, comparable to currently approved once-daily INSTIs[1]
- PK data indicate GS-3242 can be administered as a long-acting injectable, with a dosing interval of at least every four months
  - Additional cohorts are underway to evaluate a higher dose with the potential for a six-month dosing interval
- Phase 2 is expected to begin this year

The combination of GS-3242 with lenacapavir has the potential to form a complete long-acting HIV-1 treatment regimen

INSTI, Integrase strand transfer inhibitor; **PK,** pharmacokinetics

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

Acknowledgements and Summary

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Please visit CROI 2026 posters 521 and 490 for more information on the pre-clinical anti-HIV-1 activity and physiochemical properties of GS-3242

Plain Language Summary

In our early studies of GS-3242, a potential new medicine for treating HIV, we found three encouraging results:
1) GS-3242 did not show concerning safety issues; 2) it helped lower the amount of HIV in the blood; 3) it stays in the body for a long time, so it may be possible for people to take GS-3242 only once every few months instead of daily