Resistance Profile of the HIV Integrase Strand Transfer Inhibitor GS-3242, a Potent Novel Long-Acting Injectable INSTI in Clinical Development

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Conclusions

- GS-3242 is a novel long-acting INSTI with greater in vitro antiviral potency than bictegravir and a similarly high barrier to resistance, demonstrated both in vitro and in people living with HIV.
- GS-3242 conferred broad coverage across an HIV-1 panel of INSTI-resistant mutants, exhibiting an in vitro resistance profile comparable to bictegravir and improved over cabotegravir.
- In vitro, GS-3242 prevented viral breakthrough at a clinically relevant concentration and selected for G193G/E in integrase in dose escalation selections with minimal impact on susceptibility to GS-3242.
- In a Phase 1b 10-day monotherapy study to test the efficacy and safety of GS-3242, there was no emergence of primary INSTI resistance-associated substitutions and no loss of phenotypic susceptibility to GS-3242 or any other approved INSTI.

Plain Language Summary

- GS-3242 is a promising investigational HIV medicine that remains fully active in cell culture against most HIV variants conferring reduced susceptibility to currently approved INSTIs and prevents the development of primary drug-resistant variants in lab-based assays.
- In a 10-day monotherapy study in people living with HIV, no new resistance emerged and the virus remained fully susceptible to GS-3242 and other medications within the same drug class.

Introduction

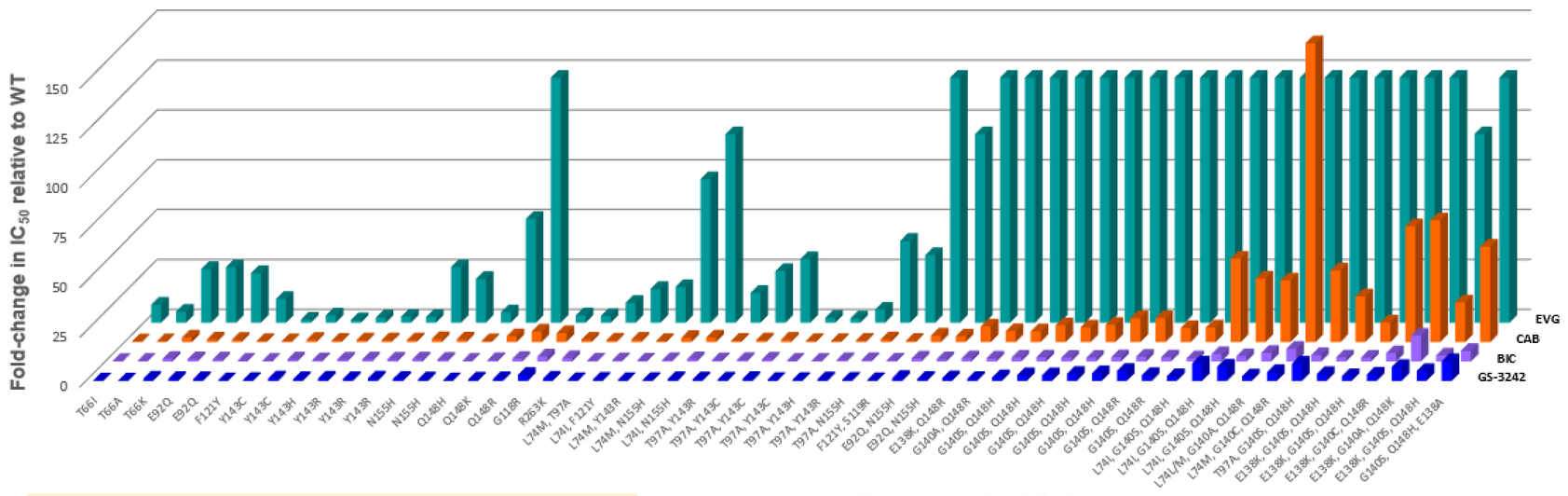
- Once-daily single tablet regimens containing an integrase strand transfer inhibitor (INSTI) remain the backbone of current oral anti-HIV therapies due to their excellent potency, tolerability and high barrier to resistance.
- For some people living with HIV (PWH), the requirement for daily oral medications remains a significant burden that can negatively impact their quality of life. To overcome this unmet medical challenge, there is strong interest in the development of long-acting therapies that can support less frequent dosing.
- GS-3242 is a novel investigational INSTI with long-acting potential that shows 3-fold improved antiviral potency relative to bictegravir (BIC)[a] and was designed to support less frequent dosing (e.g., oral once-weekly and/or injectable once every 4 or 6 months)[b] while maintaining strong antiviral activity and a favorable resistance profile.
- In a Phase 1b 10-day monotherapy study (NCT07001319)[c], GS-3242 (175 mg to 900 mg dosed orally on days 1 and 2) demonstrated robust antiviral activity with a ≥2-log_{10} decline in HIV-1 plasma RNA from baseline at Day 11 in all cohorts.
- GS-3242 in combination with lenacapavir has begun a Phase 2 study (PULSAR-1, NCT07645287) testing the efficacy of switching from Biktarvy to long-acting intramuscular injections.
- Herein we describe the in vitro resistance profile for GS-3242 along with interim resistance observations from its Phase 1b oral monotherapy study.

Methods

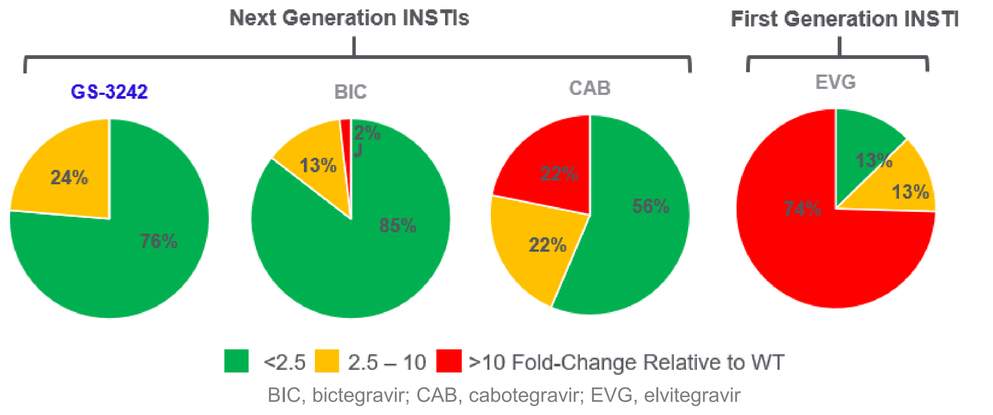
- GS-3242 antiviral activity against a panel of 55 HIV-1 reporter viruses containing integrase substitutions associated with INSTI class resistance was assessed via the PhenoSense® assay at Monogram Biosciences, Inc. (South San Francisco, USA).
- In vitro selection for drug resistant mutants was performed by dose escalation in HIV-1_{IIIb}-infected Sup-T1 cells; emergent integrase variants were sequenced and phenotyped in MT-4 cells.
- In vitro selection for drug-resistant viral variants was performed in activated human peripheral blood mononuclear cells (PBMCs) infected with HIV-1_{BaL} and cultured for 35 days in clinically relevant fixed INSTI concentrations. At weekly intervals, fresh drug and activated PBMCs were added to each well. After 35 days of selection, the integrase portion of *pol* in each sample was sequenced to determine the proportion of cultures with INSTI resistance-associated mutations.
- Study GS-US-544-5905-05 was a Phase 1b, multicohort, open-label study to evaluate GS-3242 as 10-day monotherapy in participants with untreated or unsuppressed (INSTI-naïve) HIV-1 infection.
- All participants dosed with GS-3242 who completed 39 days of follow-up (n=17) were included in the resistance analyses.
- Day 1 (baseline) and Day 11 samples from all participants were tested for genotypic and phenotypic resistance to GS-3242 and other INSTIs at Monogram Biosciences, Inc.

Results

GS-3242 Shows Broad Coverage of INSTI-resistant HIV-1 Mutants



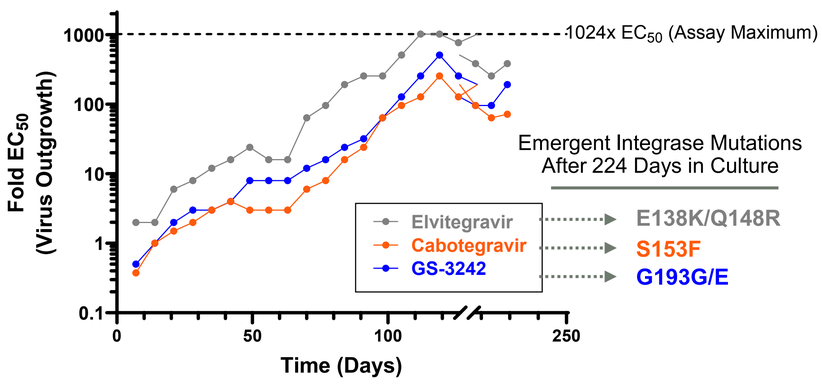
- GS-3242 in vitro resistance profile is comparable to BIC and improved relative to CAB and 1st gen INSTIs
- No high-level resistance (>10 fold) to GS-3242 was observed for any INSTI-r isolates from this diverse pool of mutants



BIC, bictegravir; CAB, cabotegravir; EVG, elvitegravir

GS-3242 Does Not Select for Primary INSTI-resistant Mutations In Vitro

Virus Outgrowth Kinetics and Emergent Integrase Variants:

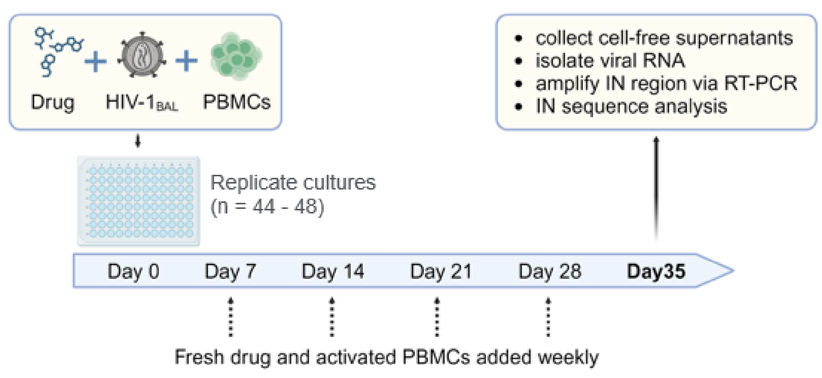


Phenotype

Compounds	EC_{50} in nM (Fold-Change Relative to WT)			
	WT HXB2	IN-G193E	IN-S153F	IN-E138K/Q148R
GS-3242	1.6 ± 0.2 (1.0)	2.3 ± 0.3 (1.4)	2.4 ± 0.4 (1.5)	3.0 ± 0.5 (1.9)
Cabotegravir	2.6 ± 0.2 (1.0)	3.9 ± 0.4 (1.5)	4.8 ± 0.1 (1.9)	11 ± 1 (4.5)
Elvitegravir	10 ± 2 (1.0)	13 ± 1 (1.3)	18 ± 3 (2.0)	692 ± 224 (68)

2.5 – 10 >10 Fold-Change Relative to WT

GS-3242 Prevents Viral Breakthrough At Clinically Relevant Drug Concentrations

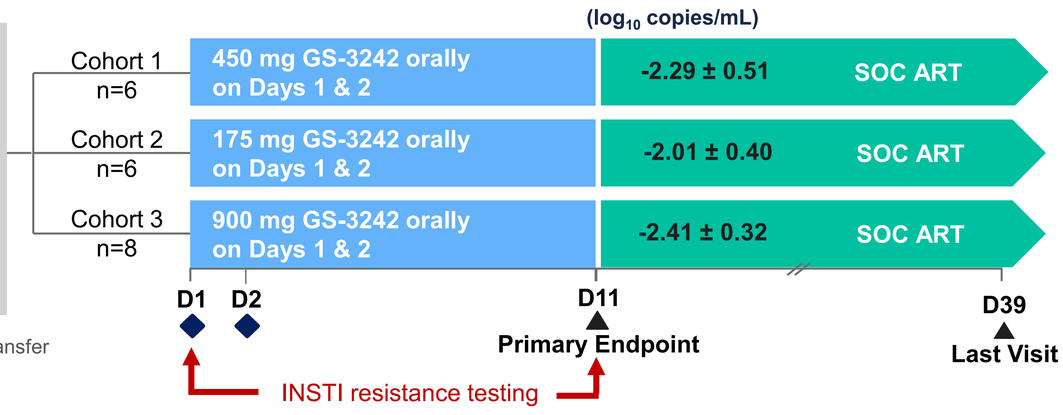


INSTIs	Viral Breakthrough in HIV-1_{BaL}-Infected Human PBMCs at Fixed INSTI Concentrations			
	Fixed nM Drug Concentration (IQ)[a]	Fraction of Samples with Breakthrough	Breakthrough Frequency (%)	Integrase Mutations (No.)
GS-3242	8.2 (2.7)	0 / 48	0	N/A
Bictegravir	29 (3.1)	0 / 48	0	N/A
Raltegravir	60 (tissue culture equivalent C_{min})	9 / 44	21	N155H (3), Q148R (3), Q148H (1), Q148K (1), E138K (1)
Elvitegravir	48 (tissue culture equivalent C_{min})	18 / 44	41	R263K (4), T66I (3), N155H (2), G163R/S230R (2), E92G (2), T66A (1), N155S (1), D232N (1), T66I/G163R (1), Q148K (1)

[a] IQ, inhibitory quotient, is equal to 1x protein-adjusted EC_{95}

Phase 1b Study (NCT07001319) Design and Antiviral Response

Key inclusion criteria:
- Adults with HIV-1 infection
- HIV-1 RNA 5,000–400,000 copies/mL
- Treatment-naïve (or) Treatment-experienced (INSTI-naïve) and off ART ≥12 weeks
- CD4+ cell count >200 cells/mm^3



ART, antiretroviral therapy; D, day; INSTI, integrase strand transfer inhibitor; SOC, standard of care (Biktarvy)

GS-3242 Does Not Select for Primary INSTI Resistance after 10 Days of Monotherapy in PWH

Resistance Substitution(s)	Participants with Integrase Data, n (%)	
	Pre-existing at Baseline (n = 16)	Emergent at Day 11 (n = 12)[c]
Primary INSTI-r [a]	0	0
Secondary INSTI-r [b]	7 (43.8%)	1 (8.3%)
M50I	3 (18.8%)	0
L74I/M	2 (12.5%)	0
S119P/R/T	2 (12.5%)	1 (8.3%)
E157K/Q	2 (12.5%)	0

- No emergence of primary INSTI resistance substitutions; secondary INSTI resistance substitutions observed at Day 1 (baseline) and Day 11 represent common integrase polymorphisms.
- In Cohort 2 (175 mg), one participant with a -1.41 log_{10} decline in HIV-1 plasma RNA from Day 1 to Day 11 had emergent S119R at Day 11; isolates from Days 1 and 11 were fully susceptible to GS-3242, with fold changes of 1.22 and 0.96, respectively.

[a]Primary INSTI resistance substitutions: T66A/I/K, E92G/Q/V, F121C/Y, G140R, Y143C/H/R, S147G, Q148H/K/R, N155H/S, and R263K.
[b]Secondary INSTI resistance substitutions: M50I, L68I/V, 74I/M, T97A, S11P/R/T, E138A/K/T, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/I/L, S153F/Y, E157K/Q, and S230R.
[c]Insufficient viral RNA was obtained from 4 participants for sequence analysis.
INSTI, integrase strand transfer inhibitor; PWH, people with HIV-1

No Loss of Phenotypic Susceptibility to GS-3242 or any Approved INSTI after 10 Days of GS-3242 Monotherapy

	GS-3242	BIC	CAB	DTG	EVG	RAL
Day 1 to Day 11 ΔIC_{50} fold-change range	-0.32 to 0.24	-0.37 to 0.11	-1.07 to 0.55	-0.68 to 0.33	-0.94 to 0.14	-0.59 to 0.30

BIC, bictegravir; CAB, cabotegravir; DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir; IC_{50}, half maximal inhibitory concentration

References: [a] Hansen et al. CROI (2026), Poster #521; [b] Subramanian M., et al. CROI. (2026), Poster #490; [c] Gupta et al. CROI (2026), Oral #174

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