In Vitro Resistance Profile for GS-1720, a Potent Once-Weekly Oral INSTI in Clinical Development

H-01 # 724

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Conclusions

- GS-1720 is a novel investigational oral INSTI with improved antiviral potency compared to best-in-class INSTI bictegravir (BIC) and a high barrier to in vitro resistance.
- GS-1720 shows broad coverage against a diverse panel of INSTI resistant clones with an in vitro resistance profile comparable to BIC and improved over cabotegravir (CAB).
- GS-1720 prevents viral breakthrough at clinically relevant drug concentrations. At subtherapeutic INSTI concentrations, GS-1720 and bictegravir each select for S153Y/F integrase variants conferring low-level INSTI resistance.
- These data support the ongoing clinical development of GS-1720 as a first-in-class, once-weekly oral INSTI for the treatment of HIV-1 infection in combination with the oral lenacapavir prodrug GS-4182.

Introduction

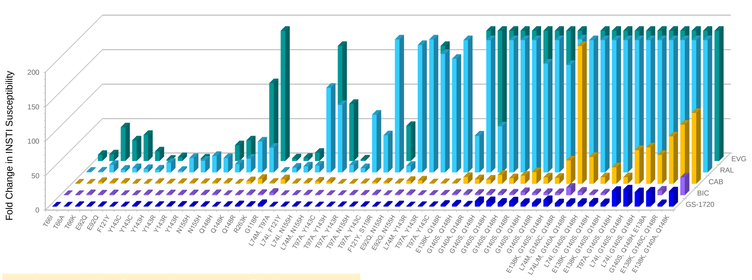
- Once daily single tablet regimens containing an integrase strand transfer inhibitor (INSTI) remain the standard-of-care treatment option for people with HIV (PWH) given their high barrier to resistance and favorable safety profile.
- For some portion of PWH, the requirement for daily oral medications 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 longer acting oral therapies that can be administered less frequently.
- GS-1720 is a potent and selective investigational INSTI in clinical development as a novel once-weekly oral antiretroviral for the treatment of HIV-1 infection in combination with GS-4182[1].
- GS-1720 has demonstrated a pharmacokinetic profile supportive of weekly oral dosing[2]. In a pivotal Ph1b study (NCT05585307, Study GS-US-544-5905-02), 450 mg GS-1720 dosed once daily on day 1 and 2 showed robust antiviral efficacy with a mean plasma HIV-1 RNA decline of >2 log_{10} copies/mL by day 8 of monotherapy[3].
- Herein we describe the in vitro resistance profile for GS-1720.

Methods

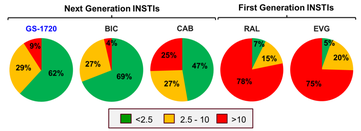
- GS-1720 antiviral activity against a panel of 55 HIV-1 reporter viruses containing integrase substitutions associated with INSTI class resistance was assessed via the PhenoSense® assay at Monogram Biosciences, Inc.
- In vitro selection for drug-resistant viral variants was performed in activated human 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 PBMCs were added to each well. After 35 days of selection, the integrase portion of *pol* was sequenced to determine the proportion of cultures with INSTI resistance-associated mutations.
- In vitro selection for drug-resistant HIV-1 was also performed by serial passage of HIV-1_{IIIb}-infected MT-2 cells cultured in the presence and absence of incrementally increased concentrations of INSTIs over a period of 4 to 12 months. Final passaged viruses were amplified, the integrase region sequenced and phenotyped using a 5-day cytopathic antiviral assay in MT-2 cells.
- MT-2 cells infected with clonal HIV-1_{HXB2} (WT and G140S/Q148H integrase mutant) were serially passaged in duplicate in the presence and absence of incrementally increased concentrations of GS-1720 using an automated platform. Viral outgrowth was monitored via weekly infectivity measurements in CEM-NKr-LTR-Luc+ indicator cells and the integrase portion of *pol* sequenced after 56, 112 and 168 days of selection.
- Clonal site-directed mutant HIV-1_{HXB2} viruses encoding emergent integrase mutations were phenotyped using a 5-day luminescence-based antiviral assay in CEM-NKr-LTR-Luc+ cells.

Results

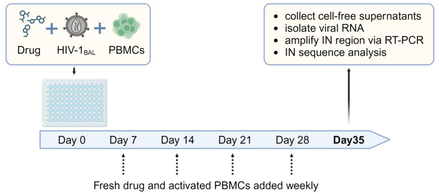
GS-1720 Shows Broad Coverage of INSTI-r HIV-1 Mutants



- GS-1720 in vitro resistance profile is comparable to BIC and improved relative to CAB, RAL and EVG
- High-level resistance to GS-1720 requires at least 3 IN mutations (G140A/S + Q148H/K +L74I, T97A or E138A/K)



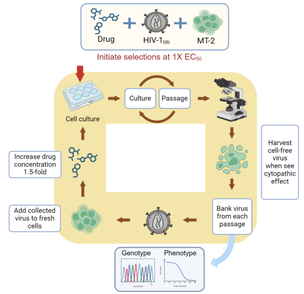
GS-1720 Prevents Viral Breakthrough in PBMCs



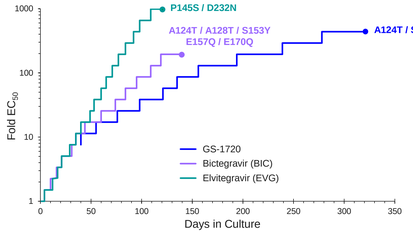
INSTIs	Viral Breakthrough in HIV-1_{BaL}-Infected Human PBMCs at Fixed INSTI Concentrations			
	Fixed nM Drug Concentration (IQ)	Fraction of Samples with Breakthrough	Breakthrough Frequency (%)	Integrase Mutations (No.)
GS-1720	6.2 (2.5)	0 / 48	0	N/A
Bictegravir	30 (2.5)	0 / 48	0	N/A
Raltegravir	60 (tissue culture equivalent C_{min})	8 / 44	18	T66A/K (2), E92A (1), T97A (1), Q148R (1), V151I (3), N155H (1)
Elvitegravir	48 (tissue culture equivalent C_{min})	20 / 44	45	T66I/A (8), E92A/G/Q (4), S153A (2), N155H/S (6), R263K (3)

GS-1720 and Bictegravir Select for HIV-1_{IIIb} S153 Integrase Variants in MT-2 Cells

Assay protocol:



Viral outgrowth kinetics & emergent integrase mutations:

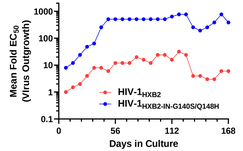


Drug susceptibility of final selected viral passages in MT-2 cells:

Compound (Class)	EC_{50} Fold-Change (relative to WT)			
	HIV-1_{IIIb} input virus	Selected HIV-1_{IIIb} Virus Passage (P)		
		GS-1720, P-16	BIC, P-14	EVG, P-18
GS-1720 (INSTI)	1.0 ± 0.1	9.0 ± 2.5	2.8 ± 0.4	0.6 ± 0.1
Bictegravir (INSTI)	1.0 ± 0.1	6.8 ± 1.8	4.4 ± 0.9	0.5 ± 0.1
Elvitegravir (INSTI)	1.0 ± 0.1	6.0 ± 1.3	1.8 ± 0.3	63 ± 19
Efavirenz (NNRTI, control)	1.0 ± 0.2	2.1 ± 0.3	0.6 ± 0.1	0.9 ± 0.2

Clonal HIV-1_{HXB2} Dose Escalation Selections

- GS-1720 selects for S153Y in clonal WT selections, and T97A using the G140S/G148H integrase mutant (~0.1% prevalence in circulating isolates)



Compound	Selected Virus (HIV-1_{HXB2})	Selection Replicate	Integrase Mutations Drug Concentration Reached (nM) (Fold EC_{50})		
			Day 56	Day 112	Day 168
GS-1720	WT Integrase (IN)	1	none 5.5 (8)	S153Y 11.0 (16)	none 2.8 (4)
		2	S153S/Y 5.5 (8)	S153Y 11.0 (16)	A21A/T 5.5 (8)
	IN-G140S/ Q148H	1	+T97A 353 (512)	+T97A, V72V/I, P233P/Q 177 (256)	+T97A 177 (256)
		2	+T97A 353 (512)	+T97A 707 (1,024)	+T97A, V72I, G149A 353 (512)

HIV-1_{HXB2} Site-Directed Integrase Mutant Profiling

Compound (Class)	HIV-1_{HXB2} WT EC_{50} (nM)	EC_{50} Fold-Change (relative to WT)					
		P145S	S153F	S153Y	T97A	G140S/Q148H	G140S/Q148H/T97A
GS-1720 (INSTI)	0.3 ± 0.1	0.3 ± 0.0	0.7 ± 0.3	1.5 ± 0.5	0.4 ± 0.1	6.8 ± 1.4	121 ± 47
Bictegravir (INSTI)	0.8 ± 0.1	0.2 ± 0.0	0.9 ± 0.8	1.5 ± 0.5	0.6 ± 0.2	2.3 ± 0.4	5.8 ± 0.7
Cabotegravir (INSTI)	0.4 ± 0.1	0.2 ± 0.0	1.3 ± 0.8	2.1 ± 0.3	0.7 ± 0.1	8.2 ± 1.7	38 ± 15
Dolutegravir (INSTI)	0.6 ± 0.1	0.2 ± 0.0	0.6 ± 0.4	1.9 ± 0.3	0.5 ± 0.1	4.4 ± 1.0	7.5 ± 2.3
Elvitegravir (INSTI)	1.1 ± 0.3	31 ± 6	1.2 ± 0.3	2.7 ± 0.4	2.5 ± 1.3	>456	>456
Efavirenz (NNRTI, control)	0.6 ± 0.1	1.8 ± 0.1	0.5 ± 0.2	1.1 ± 0.2	0.6 ± 0.2	1.2 ± 0.1	0.9 ± 0.1

- S153F/Y and T97A integrase variants are highly susceptible to GS-1720 and other INSTIs

NNRTI, non-nucleoside reverse transcriptase inhibitor

References: **1.** Hanen D, et al. *International AIDS Conference.* 2024, Poster THPEA025; **2.** Zhang H, et al. *International AIDS Conference.* 2024, Poster WEPEB116; **3.** Fichtenbaum CJ, et al. *CROI.* 2024, Oral Presentation #116.

Disclosures: All authors are current or former employees of and own stock in Gilead Sciences, Inc.

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