Nonclinical Pharmacology Profile of GS-1720, a Novel, Highly Potent, Once-Weekly Oral HIV-1 Integrase Strand Transfer Inhibitor in Clinical Development

Poster # THPEA025

Derek Hansen, Gary Lee, Eric Singer, Ellie Babakan, Joseph Campbell, Michael Lee, Yili Xu, Rolando Mejorado, Shekeba Ahmadyar, George Stepan, Ruoyu Gong, Annapurna Sapre, Bruno Marchand, Julie Chan, Nikolai Novikov, Gregg Schwarzwalder, Anita Niedziela-Majka, Helen Yu, Andrew Mulato, Supriya Kulkarni, Ana Z. Gonzalez, Tomas Cihlar and Stephen R. Yant

Gilead Sciences, Inc., Foster City, California, 94404, USA

QR code to be replaced with new one specific to a poster

Conclusions

- GS-1720 is a novel oral INSTI with significantly improved antiviral potency compared to bictegravir and a similar nonclinical virology, pharmacology and safety profile.
- These data support the ongoing clinical development of GS-1720 as a potential first-in-class, once-weekly oral INSTI for the treatment of HIV-1 infection.

Background

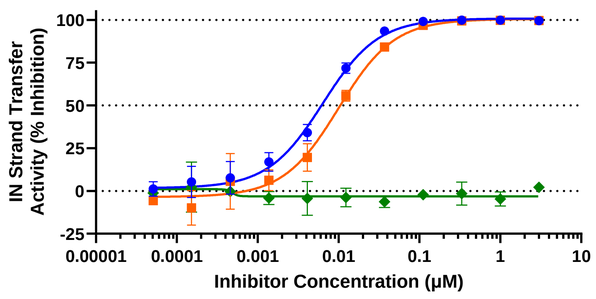
- Once daily single tablet regimens containing an integrase strand transfer inhibitor (INSTI) remain the standard-of-care treatment option for people with HIV (PWH) (1).
- For some PWH, for whom once daily oral medications remains a significant burden and unmet medical challenge, there is strong interest in developing longer acting oral and injectable therapies to meet their needs.
- 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.
- GS-1720 was found to be well tolerated in healthy volunteers, with a median half-life ($t_{1/2}$) of 9.3 days supportive of weekly dosing (2).
- In a Ph1b study, GS-1720 (450 mg) dosed once daily on Day 1 and Day 2 showed robust antiviral efficacy in PWH, with a mean plasma HIV-1 RNA decline of >2.0 $\log_{10}$ copies/mL by Day 8 of monotherapy (3).
- Herein we describe the in vitro pharmacology and nonclinical safety/toxicology profiles for GS-1720.

Methods

- Integrase strand transfer activity was measured in an enzymatic assay with recombinant HIV-1 IN.
- Antiviral activity was measured in isolated primary human immune cells infected with HIV-1 BaL strain by p24 ELISA and in PBMCs infected with clinical HIV-1 and HIV-2 isolates using a radiolabeled reverse transcriptase (RT) assay.
- Drug susceptibility to HIV-1 strains with and without site-directed INSTI-r, NRTI-r, NNRTI-r, PI-r, or CAI-r mutations was assessed in antiviral (MT-2) assays.
- In vitro selection for drug resistant HIV was performed by dose escalation.
- Pairwise in vitro drug combinations were assessed in HIV-1_{IIIb}-infected MT-2 cells and the antiviral combination effect evaluated using SynergyFinder Plus.
- GS-1720 was tested for antiviral activity against 4 non-HIV viruses.
- Compound cytotoxicity was assessed in primary and immortalized human cell lines of different tissue origin over a period of 5-11 days using CellTiter-Glo.
- Potential for off-target binding activity was assessed using a panel of 87 molecular targets including receptors, ion channels, transporters and enzymes.
- Safety pharmacology and toxicology profiles were evaluated in vitro and in nonclinical species (rat, monkey) following oral GS-1720 administration.

Results

GS-1720 is a Potent Inhibitor of HIV-1 Integrase (IN) Strand Transfer Activity In Vitro



Antiviral	Class	IC_{50} (nM)[a]
GS-1720	INSTI	6.2 ± 0.4
Bictegravir	INSTI (pos control)	10.0 ± 1.0
Atazanavir	PI (neg control)	>3,000

a Mean ± SD values from 3 experiments assayed in quadruplicate

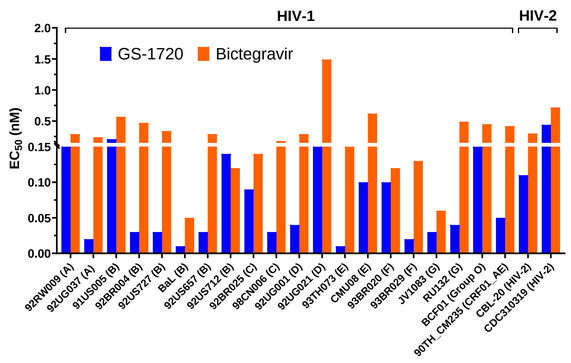
Results

GS-1720 is a Potent and Selective Inhibitor of HIV-1 Replication in Primary Human Target Cells

	CD4+ T-Lymphocytes			Monocyte-derived Macrophages		
	EC_{50} (nM)[a]	CC_{50} (μM)[a]	SI[b]	EC_{50} (nM)[a]	CC_{50} (μM)[a]	SI[b]
GS-1720	0.76 ± 0.25	14.6 ± 2.1	19,200	0.79 ± 0.40	10.4 ± 0.7	13,100
	7.5X			3.5X		
Bictegravir	5.73 ± 1.33	9.6 ± 2.3	1,680	2.60 ± 0.24	43.6 ± 0.7	16,800

a Mean ± SD values from 4 independent donors assayed in triplicate; P = 0.003 for both cell types (potency) by unpaired t-test
b SI, selectivity index (CC_{50}/EC_{50} ratio)

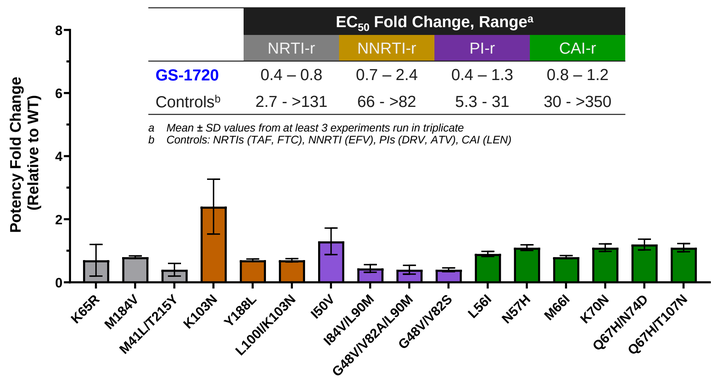
GS-1720 Shows High Potency Against a Multiclade Panel of HIV Clinical Isolates in Human PBMCs



	HIV-1 EC_{50} (nM, n=20)			HIV-2 EC_{50} (nM, n=2)
INSTI	Mean ± SD	Median	Range	Mean (range)
GS-1720	0.07 ± 0.06	0.04	0.01 - 0.21	0.28 (0.11 - 0.44)
	4.9X	7.3X		
Bictegravir	0.34 ± 0.32	0.29	0.05 - 1.49	0.51 (0.30 - 0.72)

Mean, median and range values from single mixture of PBMC donors assayed in triplicate; P < 0.001 (HIV-1) and P = 0.47 (HIV-2) by unpaired t-test

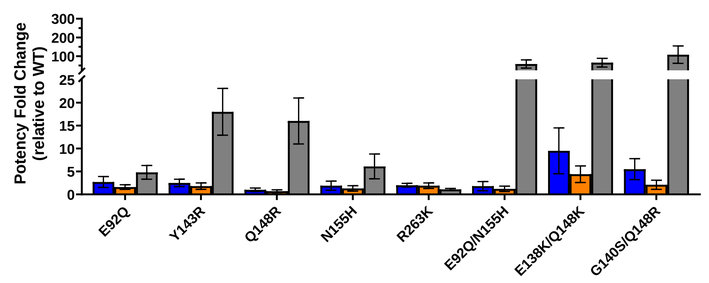
GS-1720 Shows Full Antiviral Potency Against a Panel of HIV-1 Mutants Resistant to Other Drug Classes



	EC_{50} Fold Change, Range[a]			
	NRTI-r	NNRTI-r	PI-r	CAI-r
GS-1720	0.4 – 0.8	0.7 – 2.4	0.4 – 1.3	0.8 – 1.2
Controls[b]	2.7 - >131	66 - >82	5.3 - 31	30 - >350

a Mean ± SD values from at least 3 experiments run in triplicate
b Controls: NRTIs (TAF, FTC), NNRTI (EFV), PIs (DRV, ATV), CAI (LEN)

GS-1720 Retains Activity Comparable to Bictegravir Against Common INSTI-r Site-Directed HIV-1 Mutants



	Mean EC_{50} Fold Change (relative to WT)[a]							
	E92Q	Y143R	Q148R	N155H	R263K	E92Q/ N155H	E138K/ Q148K	G140S/ Q148R
GS-1720	2.7	2.5	1.0	1.9	2.0	1.8	9.5	5.5
Bictegravir	1.6	1.8	0.7	1.3	1.9	1.2	4.4	2.1
Raltegravir	4.8	18	16	6.1	1.1	58	65	108

a Mean FC values (± SD, in bar graph) from at least 3 independent experiments assayed in quadruplicate

GS-1720 Shows No Clinically Relevant Antiviral Activity Against Several Non-HIV Viruses

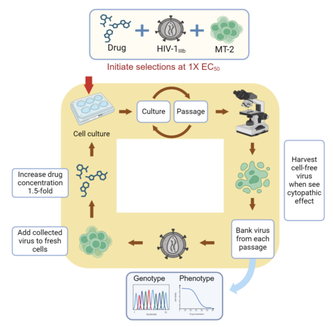
	Antiviral Activity, EC_{50} (nM)[a]			
	HCV	HBV	SARS-CoV-2	HSV-2
GS-1720	31,700 ± 1,550	>50,000	>50,000	>50,000
Control (Inhibitor)	3.6 ± 3.5 (Danoprevir)	52 ± 15 (RG-7834)	37 ± 13 (Remdesivir)	121 ± 57 (Amenamevir)

a Mean ± SD values from at least 3 experiments assayed in quadruplicate

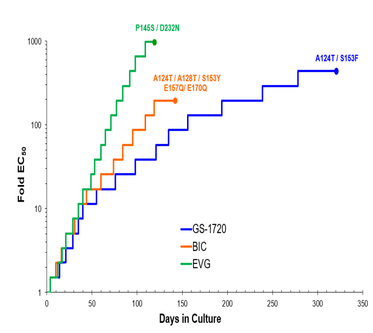
GS-1720 clinical data presented in poster WEPEB116 (ref 2)

GS-1720 and Bictegravir Select for S153 Variants In Vitro, Conferring Low-level Drug Resistance

Resistance Selection Methodology



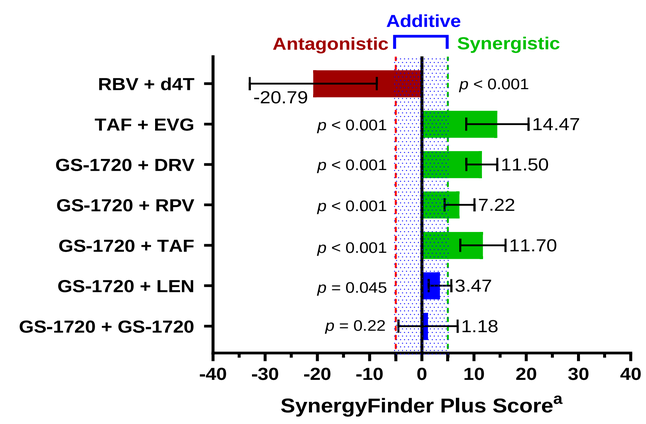
Viral Outgrowth Progression



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

a Mean ± SD values from at least 2 (BIC and EVG) or 3 (GS-1720) experiments assayed in triplicate
b A non-INSTI (NNRTI) control

GS-1720 Shows No In Vitro Antiviral Antagonism When Combined with Other Antiretrovirals



a Mean LOEWE scores from at least 14 experiments assayed in quadruplicate

GS-1720 Shows Low Cytotoxicity In Vitro Across Human Cell Lines and Primary Human Cells

Target Cells	Human Cells	Tissue Origin	Cytotoxicity, CC_{50} (μM)[a]	
			GS-1720	Puromycin
Immortalized Cell Lines	Huh-7	Hepatoma	>44	0.3 ± 0.1
	Gal-Hep-G2	Hepatoma, galactose-adapted	30 ± 8	0.5 ± 0.3
	Gal-PC-3	Prostate Carcinoma, galactose-adapted	>44	0.3 ± 0.1
	MRC-5	Embryonic Lung Fibroblast	>44	0.3 ± 0.1
Primary Cells	Hepatocytes	Liver Donors (n=3), freshly isolated	>50	0.8 ± 0.2
	Activated PBMCs	Blood Donors (n=4), IL-2/PHA-treated	9 ± 1	0.7 ± 0.1
	Unstimulated PBMCs	Blood Donors (n=4), resting	28 ± 5	0.6 ± 0.1
	CD4+ T Lymphocytes	Blood Donors (n=4), purified	15 ± 2	0.7 ± 0.1
	Macrophages	Blood Donors (n=4), monocyte-derived	10 ± 1	5.9 ± 1.5

a Mean ± SD values from at least 3 experiments assayed in quadruplicate

GS-1720 Was Well Tolerated In Nonclinical Safety Studies Up to the Highest Dose Levels Tested

Safety pharmacology studies	Outcome
Safety panel (n=87 targets)	Melanocortin receptor 4 (MC4; IC_{50} 5.11 μM)
Rat neurobehavioral function	• No GS-1720 related observations • NOEL= 300 mg/kg (highest dose tested)
Monkey cardiovascular and respiratory function	• No GS-1720 related observations • NOEL= 30 mg/kg (highest dose tested)
hERG potassium channel	IC_{50} > 6 μM (limit of solubility)

Genetic toxicity studies	Outcome
Ames, Chromosomal aberration (in vitro)	Non-mutagenic
Rat repeat dose micronucleus (in vivo)	No micronucleus formation

Repeat-dose studies	Outcome
Rat, 6-week	• No GS-1720 related adversity or target organ toxicity • NOAEL= 300 mg/kg/week (highest dose tested)
Monkey, 6-week	• No GS-1720 related adversity or target organ toxicity • NOAEL = 30 mg/kg/day (highest dose tested)

NOAEL, No observed adverse events level

References
1. DHHS guidelines on integrase strand transfer inhibitor–based regimens, updated Sept 21, 2022
2. Haeyoung Zhang, Mutaz Jaber, Eva Mortensen, Hui Wang, Ines Mendes, Monika Sobczyk, Aaron Share, Ramesh Palaparthy and Dhananjay Marathe. Phase 1a Safety and Pharmacokinetics of Single Ascending Doses of Oral GS-1720 in People Without HIV-1. *25th International AIDS Conference*, Munich, Germany, July 22-26, 2024. Poster WEPEB116.
3. Carl J. Fichtenbaum, Mezgebe Berhe, Jose Bordon, Jacob P. Lalezari, Godson Oguchi, Gary Sinclair, Furong Wang, Brie Falkard, Haeyoung Zhang, Eva Mortensen, Jared Baeten and Moti Ramgopal. Antiviral Activity, Safety, and Pharmacokinetics of GS-1720: A Novel Weekly Oral InSTI. *30th International Conference on Retroviruses and Opportunistic Infections*, Denver, CO, March 3-6, 2024. Oral #116.

Acknowledgments: This study was funded by Gilead Sciences, Inc. Resistance selection schematic was created using BioRender.

Correspondence: derek.hansen@gilead.com

Disclosures: All authors are current or previous employees of Gilead Sciences and received salary and stock ownership as compensation for their employment. The authors otherwise declare no potential conflicts of interest.

Presented at AIDS 2024, the 25th International AIDS Conference, July 22-26, Munich, Germany