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Safety and Antiviral Activity Over 10 Days Following a Single Dose of Subcutaneous GS-6207, a First-in-Class, Long-Acting HIV Capsid Inhibitor in People Living With HIV

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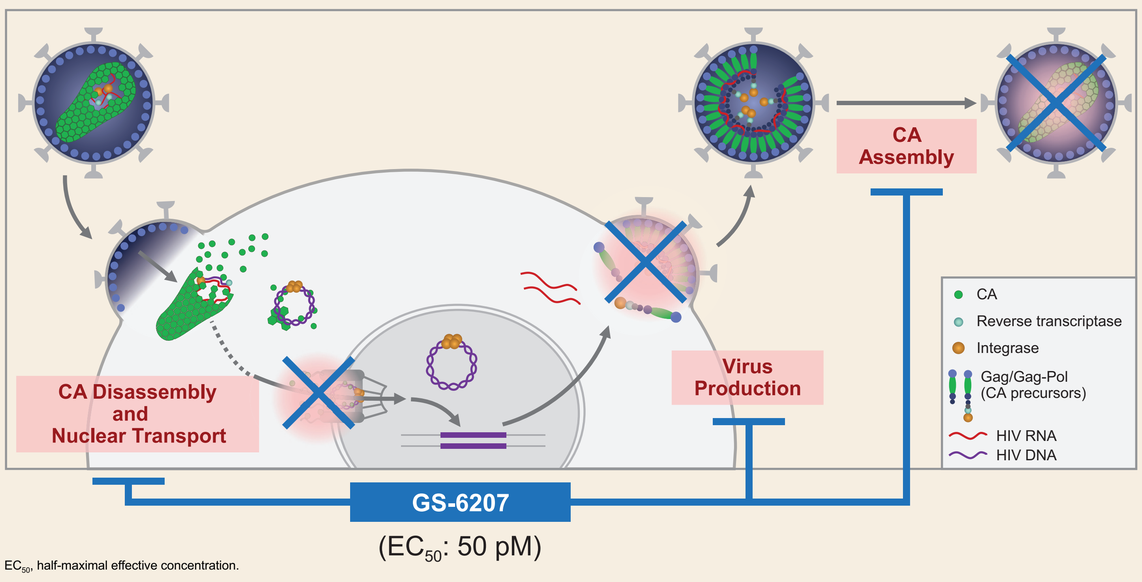
Introduction

- GS-6207 is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid (CA) function
- GS-6207 can meet significant unmet medical needs for:
  - Antiretrovirals (ARVs) with a novel mechanism of action
  - Heavily treatment-experienced people living with HIV
  - ARVs that require less frequent dosing (ie, long-acting ARVs)
- In an in vitro study, GS-6207 showed a unique resistance profile that does not overlap with any existing ARVs[1]
- In a previous clinical study in HIV-negative healthy participants, single subcutaneous (SC) doses of GS-6207 up to 450 mg were well tolerated and maintained systemic exposure for over 24 weeks[2]
- We now report the antiviral activity and safety of SC GS-6207 in people living with HIV
  - Safety data are currently blinded and are reported by cohort

GS-6207: First-in-Class HIV Capsid Inhibitor



EC_{50}, half-maximal effective concentration.

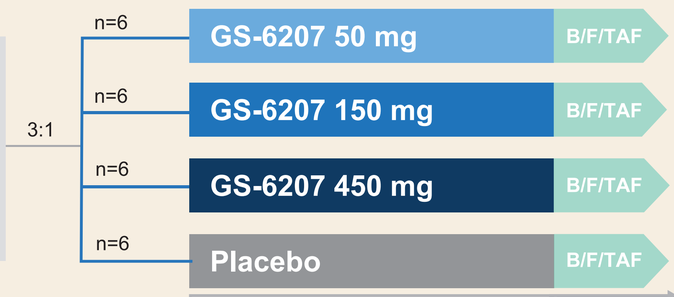
Objectives

- **Primary:** to assess the efficacy of GS-6207 in reducing plasma HIV-1 RNA over 10 days after a single dose
- **Secondary:** to assess the safety and tolerability of GS-6207

Methods

Study Designs

Key inclusion criteria:
- HIV-1 RNA 5000–400,000 copies/mL
- CD4 + cell count >200 cells/mm^3
- Naïve to capsid and integrase inhibitors



B, bictegravir; CD4, cluster of differentiation-4; F, emtricitabine; TAF, tenofovir alafenamide.

- Phase 1b, double-blind, randomized, placebo-controlled, dose-ranging study (ClinicalTrials.gov NCT03739866)
- Primary endpoint: maximum reduction of plasma HIV-1 RNA through Day 10
  - Secondary endpoint: safety and tolerability of GS-6207
- All participants were required to start B/F/TAF on Day 10
- Antiviral activity data were unblinded; safety data remain blinded given that GS-6207 was detectable for over 6 months in HIV-negative subjects in a previous clinical study[2]

Results

Duration of Follow-Up*

Days	GS-6207 50 mg or Placebo n=8	GS-6207 150 mg or Placebo n=8	GS-6207 450 mg or Placebo n=8	Total N=24
Mean (SD)	33 (6)	90 (16)	27 (11)	50 (31)
Median	32	102	25	39
Q1, Q3	28, 39	72, 102	18, 39	28, 72
Min, Max	25, 39	67, 102	16, 39	16, 102

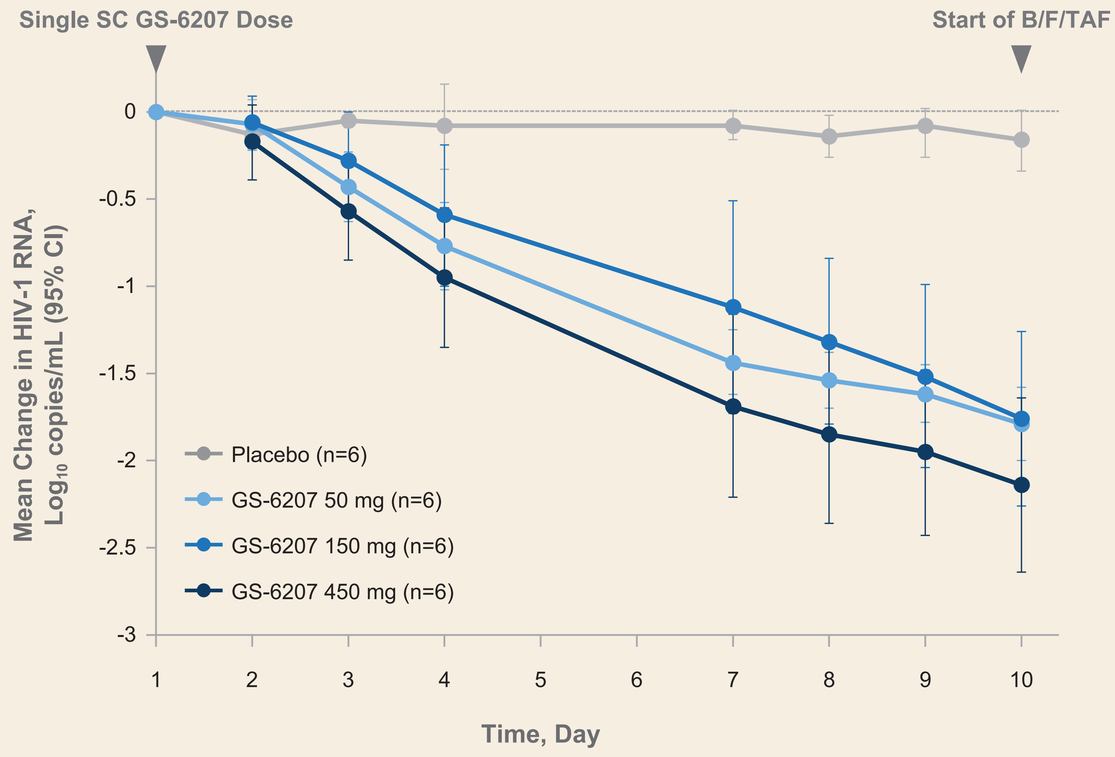
*Data were pooled from the 6 active and 2 placebo participants in each cohort as data are currently blinded. Max, maximum; Min, minimum; Q, quartile; SD, standard deviation.

Demographics and Baseline Characteristics*

		GS-6207 50 mg or Placebo n=8	GS-6207 150 mg or Placebo n=8	GS-6207 450 mg or Placebo n=8	Total N=24
Age, years		28 (19–56)	36 (24–56)	29 (20–59)	34 (19–59)
Female		0	1 (13)	0	1 (4)
Race	White	5 (63)	4 (50)	5 (63)	14 (58)
	Black	2 (25)	3 (38)	3 (38)	8 (33)
	Asian	1 (13)	0	0	1 (4)
	Other	0	1 (13)	0	1 (4)
BMI, kg/m^2		25 (21–28)	26 (20–34)	25 (23–29)	25 (20–34)
HIV-1 RNA, log_{10} copies/mL		4.33 (4.2–4.7)	4.57 (4.3–4.6)	4.48 (4.4–4.6)	4.48 (4.3–4.6)
CD4 count, cells/µL		594 (459–662)	388 (309–581)	430 (260–611)	442 (340–661)
ARV treatment naïve		6 (75)	4 (50)	7 (88)	17 (71)

*Data were pooled from the 6 active and 2 placebo participants in each cohort as the data are currently blinded; data are median (range) or n (%). BMI, body mass index.

Subcutaneous GS-6207: Antiviral Activity



CI, confidence interval.

- No treatment-emergent resistance was detected

Antiviral Activity Through Day 10

Maximum Reduction From Baseline, Log_{10} copies/mL	GS-6207 50 mg n=6	GS-6207 150 mg n=6	GS-6207 450 mg n=6	Placebo n=6
Mean	-1.8	-1.8	-2.2	-0.2
95% CI	(-2.3, -1.3)	(-2.0, -1.6)	(-2.7, -1.7)	(-0.4, -0.1)
Median (Q1, Q3)	-1.7 (-2.3, -1.6)	-1.8 (-1.9, -1.6)	-2.2 (-2.5, -1.8)	-0.2 (-0.3, -0.1)
Min, Max	-2.4, -1.2	-2.1, -1.5	-2.9, -1.6	-0.4, -0.1

- At doses of 50 to 450 mg, mean GS-6207 concentrations on Day 10 were 1.1- to 9.9-fold higher than the protein-adjusted, 95% effective concentration for wild-type HIV-1

Safety Summary: Blinded Data

	Participants, n (%)	GS-6207 50 mg or Placebo n=8	GS-6207 150 mg or Placebo n=8	GS-6207 450 mg or Placebo n=8	Total N=24
AEs	Any AE	6 (75)	7 (88)	6 (75)	19 (79)
	Grade 3 or 4 AE	0	0	0	0
	Serious AE	0	0	0	0
	AE leading to discontinuation	0	0	0	0
	Death	0	0	0	0
Laboratory abnormalities	Grade 3 or 4	0	2 (25)	0	2 (8)

AE, adverse event.

- All AEs reported were Grade 1 or 2 in severity
- The most common AEs were mild-to-moderate reactions at the injection site (63%; n=15), all of which were self-limiting
- Grade 3 or 4 laboratory abnormalities included exercised-related creatine kinase (n=1) and asymptomatic lipase (n=1)

Conclusions

- Single SC doses of GS-6207 from 50 to 450 mg resulted in potent antiviral activity in people living with HIV
  - Mean maximum HIV-1 RNA declines ranged from 1.8 to 2.2 log_{10} copies/mL over 10 days
- In a blinded safety review, GS-6207 and placebo were generally safe and well tolerated
  - The most common AEs were self-limiting mild-to-moderate injection-site reactions
- These results support further evaluation of GS-6207 as a long-acting ARV in people living with HIV

References: **1.** Yant SR, et al. CROI 2019, poster 480; **2.** Sager JE, et al. CROI 2019, oral O-13. **Acknowledgments:** We extend our thanks to the participants, their families, and all participating study investigators and staff: D Asmuth, P Benson, M Berhe, G Crofoot, E Daar, C McDonald, A Mills, O Osiyemi, MN Ramgopal, E DeJesus, PJ Ruane, GI Sinclair. This study was funded by Gilead Sciences, Inc.

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