Single Doses of Long-Acting Capsid Inhibitor GS-6207 Administered by Subcutaneous Injection Are Generally Well Tolerated and Efficacious in People Living With HIV

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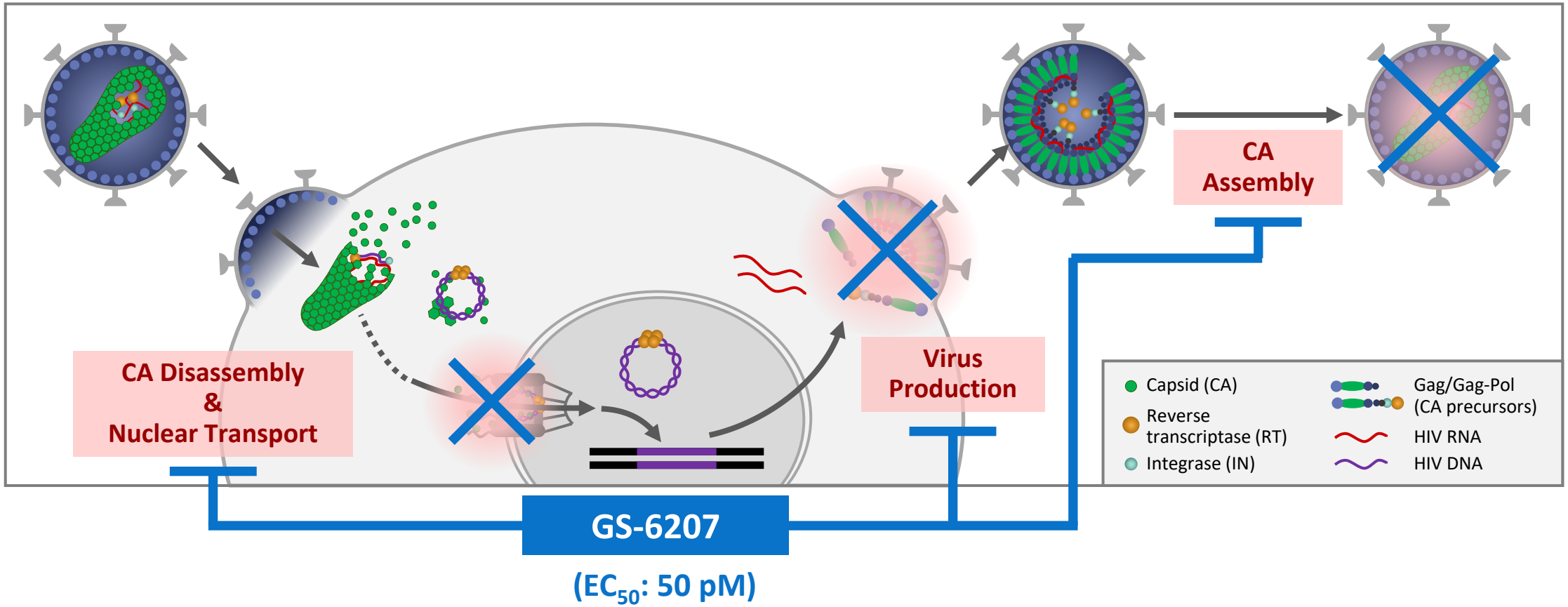
Introduction

- GS-6207 is a novel, first-in-class inhibitor of HIV-1 CA function suited for long-acting SC regimens
- GS-6207 can meet significant unmet medical needs for:
  - ARVs with a novel mechanism of action
  - Heavily treatment-experienced people living with multidrug-resistant HIV
  - ARVs that require less frequent dosing (ie, long-acting treatment) to reduce daily pill burden
- Highly desirable in vitro profile of GS-6207 for heavily treatment-experienced people[1]
  - Similar antiviral activity across all major HIV-1 subtypes
  - Unique resistance profile with full activity against NRTI-, NNRTI-, INSTI-, and HIV PI-resistant mutants[1]
- In a previous clinical study in healthy volunteers without HIV infection, single GS-6207 SC doses ≤450 mg were well tolerated and maintained systemic exposure for >32 wk[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)

ARV, antiretroviral; CA, capsid; sc, subcutaneous; INSTI, integrase strand transfer inhibitor; (N)NRTI, (non-)nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

1. Yant SR, et al. CROI 2019, poster 480; **2.** Sager JE, et al. CROI 2019, oral O-13.

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



- Inhibition of multiple CA-dependent functions essential for viral replication

EC_{50}, half-maximal effective concentration determined in peripheral blood mononuclear cells using wild-type HIV-1 patient isolates with various HIV-1 subtypes.

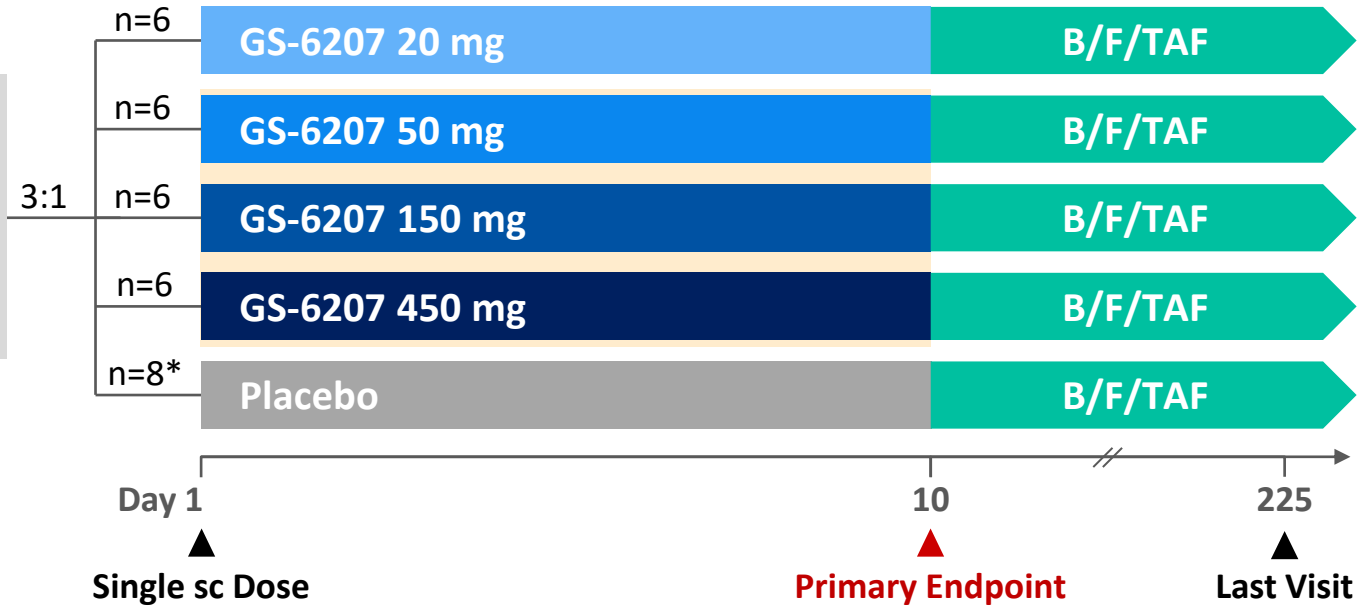
Objectives

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

Study Design

Key inclusion criteria:

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



- Phase 1b, double-blind, randomised, 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 bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) on Day 10
- Antiviral activity data were unblinded; safety data remain blinded given that GS-6207 is expected to be detectable for >6 months[2]

*The 8 participants receiving placebo consisted of 2 from each dose cohort as 8 from each dose cohort were randomised to receive either active treatment (n=6) or placebo (n=2). B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide.

Demographics and Baseline Characteristics*

	GS-6207 20 mg or PBO n=8	GS-6207 50 mg or PBO n=8	GS-6207 150 mg or PBO n=8	GS-6207 450 mg or PBO n=8	Total N=32
Median age, year (Min, Max)	35 (23, 50)	28 (19, 56)	36 (24, 56)	29 (20, 59)	34 (19, 59)
Female, n (%)	1 (13)	0	1 (13)	0	2 (6)
Race, n (%)					
White	4 (50)	5 (63)	4 (50)	5 (63)	18 (56)
Black	2 (25)	2 (25)	3 (38)	3 (38)	10 (31)
Asian	1 (13)	1 (13)	0	0	2 (6)
Other	1 (13)	0	1 (13)	0	2 (6)
Median BMI, kg/m^2 (Min, Max)	25 (21, 38)	25 (21, 28)	26 (20, 34)	25 (23, 29)	25 (20, 38)
Median HIV-1 RNA, log_{10} copies/mL (Q1, Q3)	4.5 (4.1, 4.9)	4.3 (4.2, 4.7)	4.6 (4.3, 4.6)	4.5 (4.4, 4.6)	4.48 (4.3, 4.7)
Median CD4 cells/mL (Q1, Q3)	472 (395, 542)	594 (459, 662)	388 (309, 581)	430 (260, 611)	458 (361, 594)
ARV treatment naïve, n (%)	8 (100)	6 (75)	4 (50)	7 (88)	25 (78)

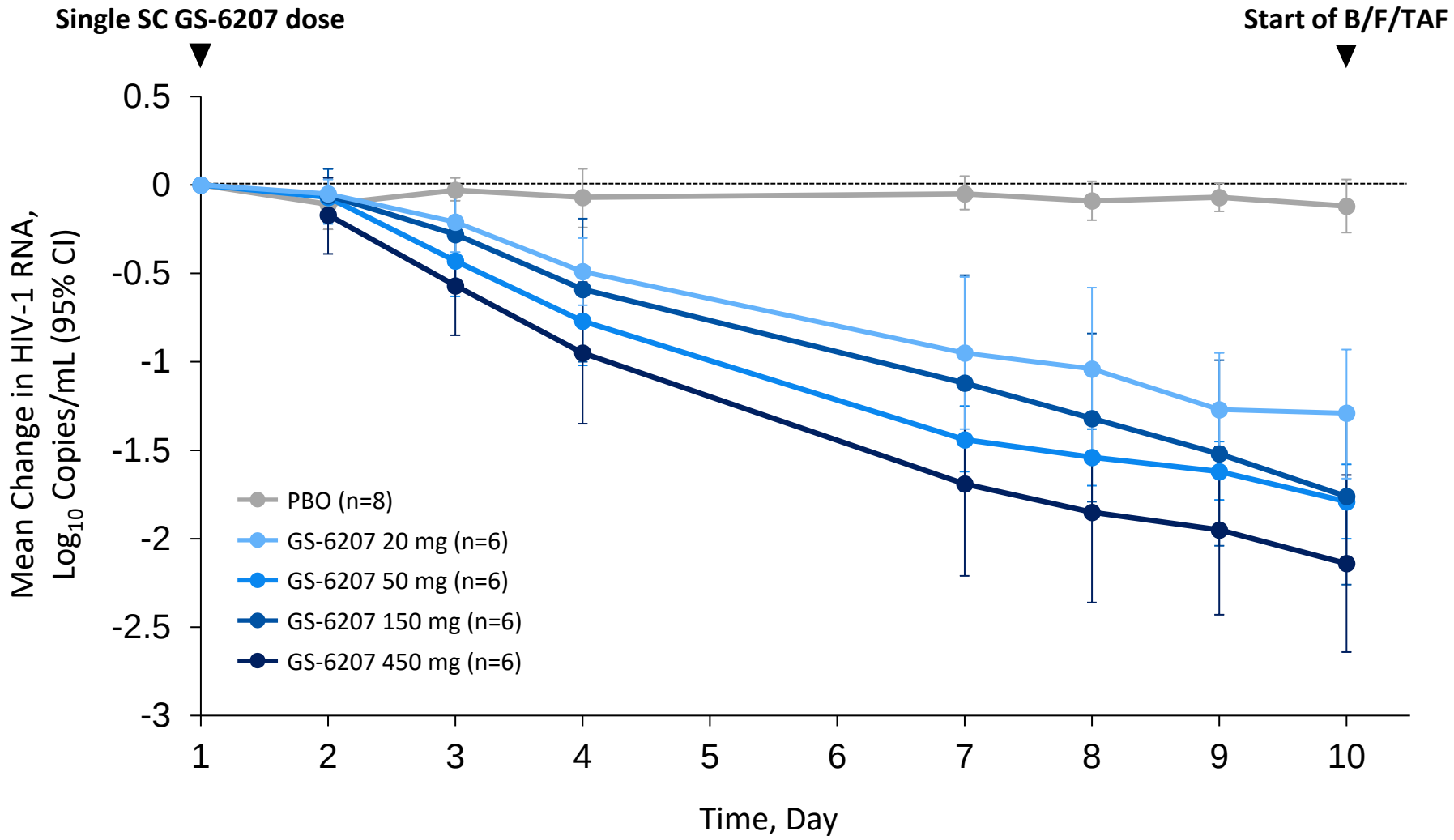
*Data were pooled from the 6 active and 2 placebo (PBO) participants in each cohort as data are currently blinded.
BMI, body mass index; Max, maximum; Min, minimum; Q, quartile.

Duration of Follow-up in Days*

	GS-6207 20 mg or PBO n=8	GS-6207 50 mg or PBO n=8	GS-6207 150 mg or PBO n=8	GS-6207 450 mg or PBO n=8	Total N=32
Mean (SD)	42 (20)	130 (6)	187 (16)	124 (11)	121 (54)
Median	38†	129	199	122	129
Q1, Q3	28, 56	125, 136	169, 199	115, 136	93, 150
Min, Max	17, 73	122, 136	164, 199	113, 136	17, 199

*Data were pooled from the 6 active and 2 PBO participants in each cohort as data are currently blinded; †Enrollment of GS-6207 20 mg randomised cohort added later in study; thus, the difference in follow-up time. SD, standard deviation.

Subcutaneous GS-6207: Antiviral Activity



CI, confidence interval.

Antiviral Activity Through Day 10

Maximum Change in HIV-1 RNA From Baseline, Log_{10} Copies/mL	GS-6207 20 mg n=6	GS-6207 50 mg n=6	GS-6207 150 mg n=6	GS-6207 450 mg n=6	PBO n=8
Mean	-1.4	-1.8	-1.8	-2.2	-0.2
95% CI	-1.7, -1.0	-2.3, -1.3	-2.0, -1.6	-2.7, -1.7	-0.3, -0.1
Median	-1.4	-1.7	-1.8	-2.2	-0.2
Q1, Q3	-1.6, -1.2	-2.3, -1.6	-1.9, -1.6	-2.5, -1.8	-0.3, -0.1
Min, Max	-1.7, -0.8	-2.4, -1.2	-2.1, -1.5	-2.9, -1.6	-0.4, 0.0

- At doses of 20–450 mg, mean GS-6207 concentrations on Day 10 were 0.7–9.9-fold higher than the protein-adjusted, 95% effective concentration for wild-type HIV-1

Safety Summary: Blinded Data

	Participants, n (%)	GS-6207 20 mg or PBO n=8	GS-6207 50 mg or PBO n=8	GS-6207 150 mg or PBO n=8	GS-6207 450 mg or PBO n=8	Total N=32
AEs	Any AE	5 (63)	6 (75)	7 (88)	6 (75)	24 (75)
	Grade 3 or 4 AE	0	0	0	1 (13)	1 (3)
	Serious AE	0	0	0	1 (13)	1 (3)
	AE leading to discontinuation	0	0	0	0	0
	Death	0	0	0	0	0
Laboratory Abnormalities	Grade 3 or 4	2 (25)	0	3 (38)	1 (13)	6 (19)

- 1 participant had a Grade 3 serious AE of atrial fibrillation on Day 113 while receiving B/F/TAF, which was not attributed to study medication; recent amphetamine use was reported; all other AEs were Grade 1 or 2 in severity
- The most common AEs were mild–moderate reactions at the injection site (50%; n=16), including pain (41%; n=13) and erythema (28%; n=9), all of which were self-limiting and resolved in a few days
- Grade 3 or 4 laboratory abnormalities in ≥2 participants were exercise-related creatine kinase elevations (n=2)

AE, adverse event.

Conclusions

- Single SC doses of GS-6207 from 20 to 450 mg resulted in potent antiviral activity in people living with HIV
  - Mean HIV-1 RNA declines from 1.4 to 2.2 $\log_{10}$ copies/mL over 10 days
- In a blinded safety review, GS-6207 and PBO were generally well tolerated
  - The most common AEs were self-limiting mild–moderate injection-site reactions
  - 1 participant had a serious AE not attributed to study medication
  - There were no clinically relevant Grade 3 or 4 laboratory abnormalities
- These results support further evaluation of GS-6207 as a long-acting ARV in people living with HIV, including those who are heavily treatment experienced

Acknowledgments

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