PE3/17

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

Eric S. Daar,[1] Cheryl McDonald,[2] Gordon Crofoot,[3] Peter Ruane,[4] Gary Sinclair,[5] Heena Patel,[6] Rebecca Begley,[6] Ya-Pei Liu,[6] Diana M. Brainard,[6] Robert H. Hyland,[6] Martin S. Rhee[6]

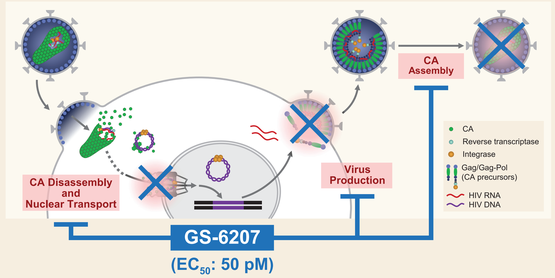
[1]The Lundquist Institute, Torrance, California, USA; [2]Tarrant County Infectious Disease Associates, Fort Worth, Texas, USA; [3]Gordon E. Crofoot MD, PA, Houston, Texas; [4]Ruane Clinical Research Group, Inc., Los Angeles, California; [5]Prism Health North Texas, Dallas, Texas; [6]Gilead Sciences, Inc., Foster City, California

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Introduction

- GS-6207 is a novel, first-in-class inhibitor of HIV-1 capsid (CA) function suited for long-acting subcutaneous (SC) regimens
- GS-6207 can meet significant unmet medical needs for:
  - Antiretrovirals (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 nucleoside reverse transcriptase inhibitor-, non-nucleoside reverse transcriptase inhibitor-, integrase strand transfer inhibitor-, and HIV protease inhibitor-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)

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



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

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

Objectives

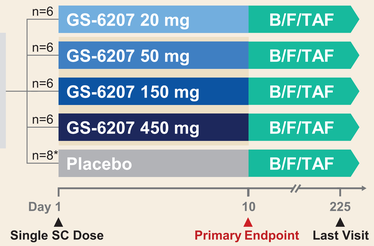
- **Primary:** to assess the antiviral activity of GS-6207 in reducing plasma HIV-1 RNA over 10 days after a single SC dose
- **Secondary:** to assess the safety and tolerability of GS-6207

Methods

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



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

Results

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)	4.5 (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)

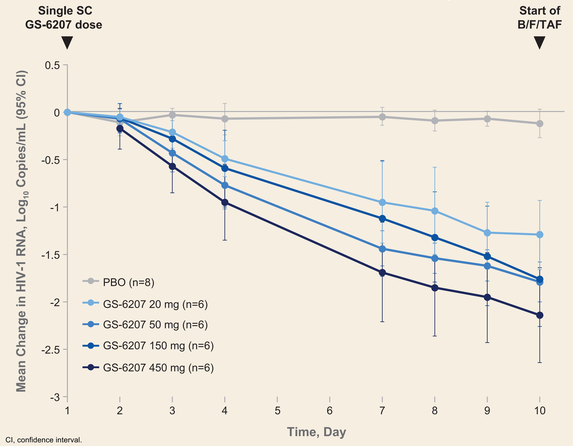
*Data were pooled from the 6 active and 2 placebo (PBO) participants in each cohort as data are currently blinded. BMI, body mass index; Max, maximum; Min, minimum; Q, quartile.

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 randomized 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
Adverse Events	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)

AE, adverse event.

- 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)

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 safe and 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

References: **1.** Yant SR, et al. CROI 2019, poster 480; **2.** Sager JE, et al. CROI 2019, abstr 141 (O-13).

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