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PK, Food Effect, and Safety of Oral GS-6207, a Novel HIV-1 Capsid Inhibitor

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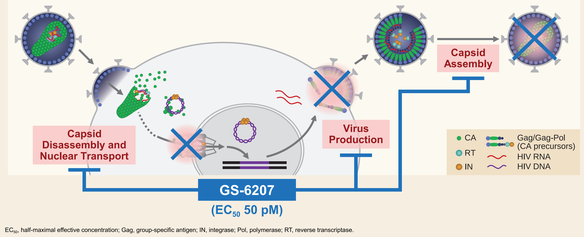
Introduction

- GS-6207 is a novel, 1st-in-class inhibitor of HIV-1 capsid (CA) function suited for long-acting regimens
- GS-6207 can meet significant unmet medical needs:
  - A new mechanism of action for heavily treatment-experienced people living with multidrug-resistant HIV
  - Reduction of daily pill burden through less frequent dosing
- Highly desirable in vitro profile of GS-6207 for heavily treatment-experienced people[1,2]
- In a previous clinical study in healthy volunteers without HIV infection, single SC doses of GS-6207 at ≥100 mg supported dosing intervals ≥12 wk[3]
- The present study assessed the single-dose pharmacokinetics (PK) and food effect of the GS-6207 oral-tablet formulation

GS-6207: 1st-in-Class HIV Capsid Inhibitor



EC_{50}, half-maximal effective concentration; Gag, group-specific antigen; IN, integrase; Pol, polymerase; RT, reverse transcriptase.

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

Objectives

- To characterize the single-dose PK of oral GS-6207 tablets
- To evaluate the safety and tolerability of escalating single oral doses of GS-6207 tablets
- To evaluate the effect of concomitant food intake on oral GS-6207 tablet PK

Methods

Study Design

	Participants, n	Fasted/Fed State	Day 1 Dose, mg
SAD	8 active and 2 placebo/cohort	Fasted	50, 300, 900, 1800
Food effect	8 active/cohort	High fat (~1000 kcal; ~50% fat) Low fat (~400 kcal; ~25% fat)	300

SAD, single ascending dose.

- SAD:
  - Randomized, blinded, placebo-controlled, SAD study in unique healthy participants
  - Participants received a single tablet dose of either GS-6207 (n=8) or placebo (n=2)
- Food effect:
  - Open-label, parallel-design, single-dose study in unique healthy participants
  - Participants received a single tablet dose of GS-6207 (n=8)
- Single-dose safety, tolerability and PK assessed throughout study
  - PK sampling performed for 64 d postdose
- Blinded safety and available PK data reviews between ascending single-dose cohorts
- Plasma concentrations of GS-6207 determined using validated liquid chromatography–tandem mass spectrometry assays
- GS-6207 PK parameters estimated using noncompartmental methods (Phoenix® WinNonlin® 7.0, Certara USA, Inc., Princeton, NJ) and summarized using descriptive statistics
- Dose proportionality assessed:
  - Regression analysis using power model
  - Analysis of variance (ANOVA), wherein 2-sided 90% confidence intervals (CIs) were constructed for geometric least-squares means (GLSMs) of dose-adjusted GS-6207 area under concentration-time curve (AUC) and maximal concentration (C_{max}), as compared with GS-6207 50 mg

Results

Participant Enrollment and Demographics

	Single Ascending-Dose Cohorts					Food-Effect Cohorts	
	GS-6207 50 mg	GS-6207 300 mg	GS-6207 900 mg	GS-6207 1800 mg	Placebo	GS-6207 300 mg High-Fat Meal	GS-6207 300 mg Low-Fat Meal
Enrolled/completed, n*	8/7	8/7	8/8	8/7	8/8	8/8	8/8
Median age, y (range)	36 (19–44)	34 (21–45)	32 (19–41)	37 (21–43)	35 (24–44)	31 (19–39)	36 (21–45)
Male, n (%)	6 (75)	4 (50)	3 (38)	5 (63)	5 (63)	4 (50)	8 (100)
White, n (%)	6 (75)	6 (75)	6 (75)	8 (100)	7 (88)	5 (63)	8 (100)
Hispanic/Latino, n (%)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	6 (75)	8 (100)
Median BMI, kg/m² (range)	26 (23–30)	23 (21–27)	25 (20–29)	29 (20–30)	27 (24–28)	25 (19–30)	27 (22–30)

*All participants completed study drug; 3 were lost to follow-up. BMI, body mass index.

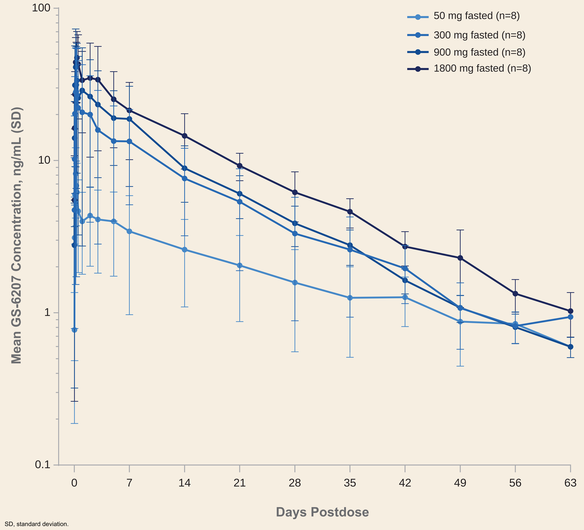
Safety

	≥2 Participants in Either Group, % (n)	GS-6207 n=48	Placebo n=8
AEs	Headache	8 (4)	13 (1)
	Oral herpes	4 (2)	0
	Back pain	2 (1)	25 (2)
Grade 3 or 4 lab abnormalities	Urine occult blood	15 (7)	0
	LDL cholesterol	2 (1)	25 (2)

AEs, adverse events; LDL, low-density lipoprotein.

- Oral GS-6207 was well tolerated in healthy participants
  - No deaths, serious AEs, or AEs leading to study drug discontinuation
  - No Grade 2–4 AEs
  - No AE related to study drug
  - No clinically relevant Grade 3 or 4 laboratory abnormalities

GS-6207 Concentration-Time Profiles: SAD Cohorts



SD, standard deviation.

Oral SAD GS-6207 Pharmacokinetic Parameters

Parameter*	50 mg n=8	300 mg n=8	900 mg n=8	1800 mg n=8
AUC_{inf}, h·ng/mL	2650 (61.0)	7990 (56.1)	9900 (44.9)	14,100 (37.5)
C_{max}, ng/mL	8.24 (48.3)	33.7 (96.3)	43.9 (73.3)	53.8 (48.0)
T_{max}, h	4.00 (4.00, 5.50)	4.00 (4.00, 6.00)	4.00 (2.50, 20.0)	8.00 (5.00, 8.00)
$t_{1/2}$, h [d]	299 (265, 453) [12.4]	265 (223, 349) [11.0]	322 (237, 333) [13.4]	311 (239, 364) [13.0]

*PK parameters presented as mean (% coefficient of variation [CV]) except time to C_{max} (T_{max}) and half-life ($t_{1/2}$), which are presented as median (quartile [Q] 1, Q3), and shown to 3 significant digits. AUC_{inf}, AUC from time 0 to ∞.

- GS-6207 T_{max} was 4–8 h postdose and median $t_{1/2}$ was ~11–13 d

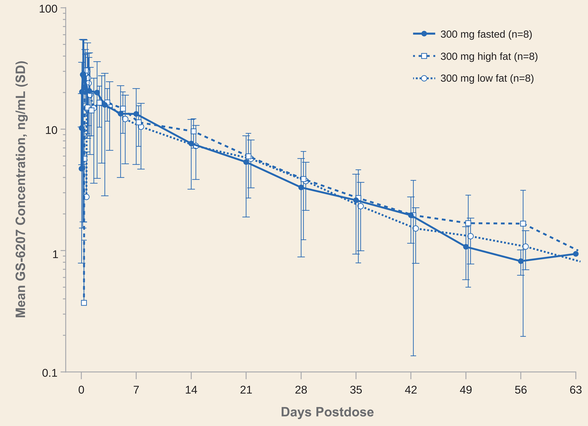
Dose-Proportionality Assessment

Parameter	Power Model Analysis Slope Ln Dose (90% CI) Across All Doses*
AUC_{inf}, h·ng/mL	0.48 (0.36, 0.59)
C_{max}, ng/mL	0.51 (0.35, 0.67)

*Power model estimates were calculated by regression of natural log-transformed PK parameter onto natural log-transformed dose; data presented to 3 significant figures.

- Per power model analysis, oral GS-6207 exposures increased in a less than dose-proportional manner from 50 to 1800 mg, which was confirmed by ANOVA (data not shown)

GS-6207 Concentration-Time Profiles: Food-Effect Cohorts



Oral Food-Effect GS-6207 Pharmacokinetic Parameters

Parameter*	300 mg Fasted n=8	300 mg + High-Fat Meal n=8†	300 mg + Low-Fat Meal n=8†
AUC_{inf}, h·ng/mL	7990 (56.1)	8060 (39.8)	7290 (49.6)
C_{max}, ng/mL	33.7 (96.3)	35.0 (33.0)	32.6 (62.4)
T_{max}, h	4.00 (4.00, 6.00)	5.00 (4.00, 6.00)	6.00 (4.00, 8.00)
$t_{1/2}$, h [d]	265 (223, 349) [11.0]	267 (236, 374) [11.1]	287 (252, 328) [12.0]

*PK parameters presented as mean (%CV), except T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits; †High-fat meal: ~1000 kcal and ~50% fat; low-fat meal: ~400 kcal and ~25% fat.

- Coadministration with a high- or low-fat meal did not affect GS-6207 PK

Conclusions

- Single doses (≤1800 mg) of GS-6207 oral tablets were generally safe and well tolerated
- Oral GS-6207 had a $t_{1/2}$ of ~11–13 d, which is supportive of less frequent dosing
- GS-6207 oral tablet exposure increases were less than dose proportional over 50–1800 mg
- GS-6207 oral tablets can be administered without regard to food
- These data support ongoing development of oral GS-6207 for use in people living with HIV in conjunction with SC GS-6207 or as part of a combination oral product with other antiretroviral agents

References: **1.** Begley R, et al. EACS 2019, oral PS-13/1; **2.** Yant SR, et al. CROI 2019, poster 480; **3.** Sager JE, et al. CROI 2019, oral O-13.
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