Safety and Pharmacokinetic Profile of Single and Multiple Ascending Doses of GS-4182, an Oral Prodrug of Lenacapavir, in Participants without HIV-1

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Conclusions

- In this Phase 1a study, GS-4182, an oral prodrug of lenacapavir (LEN), demonstrated a pharmacokinetic (PK) profile supportive of a once-weekly (QW) dosing interval
- Approximately 2-fold higher LEN relative bioavailability was observed for GS-4182 compared with historic data for direct oral LEN administration
- A single dose of GS-4182 200 mg or 600 mg rapidly achieved mean LEN concentrations above the efficacy target of inhibitory quotient 4 (IQ4) and maintained it through Day 7
- A dose-proportional increase in LEN exposure was observed following multiple QW 200 mg and 400 mg doses of GS-4182
  - After 6 weeks of QW dosing of 200 mg and 400 mg, a 6–7-fold accumulation in C_{max} and 4-fold accumulation in AUC was observed, and mean LEN concentrations remained above IQ4
- GS-4182 was well tolerated with a favorable safety profile at doses of 200 mg or 400 mg QW
- These Phase 1a PK and safety data support the future development of GS-4182 as a QW oral agent for HIV-1 treatment

Plain Language Summary

- GS-4182 is a new medicine (or drug) that is being studied for the treatment of HIV-1 infection; it is a prodrug of an existing approved HIV-1 medicine called lenacapavir
- 'Prodrug' means that, after a tablet of GS-4182 is taken by mouth, it is changed to its active form, lenacapavir, in the gut
- We studied the safety and measured lenacapavir levels in people without HIV-1 after taking a tablet of GS-4182 by mouth. Some people only took one tablet (either 200 mg or 600 mg) of GS-4182, while other people were given one tablet of a GS-4182 once a week for 6 weeks (either 200 mg or 400 mg each time)
- People who took GS-4182 once a week for 6 weeks had levels of lenacapavir in their blood higher than what is needed to work against HIV-1
- This study shows that GS-4182 could be given once a week, unlike many other HIV-1 medicines taken by mouth that need to be taken every day
- No one in the study stopped taking GS-4182 due to side effects
- Based on these results, more studies are planned to see how effective GS-4182 is at treating HIV-1 infection

Background

- LEN is a first-in-class HIV-1 capsid inhibitor approved, in combination with other antiretrovirals,, for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced people,[1,2] and is under investigation for HIV-1 pre-exposure prophylaxis
- LEN exhibits a long $t_{1/2}$ following oral administration (10–12 days); however, its absolute oral bioavailability is low (6–10%)[1,2]
- GS-4182 is a novel, oral prodrug of LEN designed to increase bioavailability of LEN
  - GS-4182 is metabolized in the gastrointestinal tract releasing LEN and metabolite Met-A[3]
  - In nonclinical studies, GS-4182 exhibited greater intestinal LEN absorption and improved systemic LEN exposure compared with oral LEN[3]

Objective

- To assess the PK and safety of single ascending doses (SAD) and multiple ascending doses (MAD) of GS-4182 in participants without HIV-1

Methods

- This randomized, blinded (sponsor unblinded), placebo-controlled, Phase 1a study enrolled participants without HIV-1 aged 18–45 years
- We report data from two SAD cohorts and two MAD cohorts:
  - In the SAD cohorts, participants received a single dose of GS-4182 200 mg or 600 mg (n=8 per cohort) or matched placebo (n=2 per cohort)
  - In the MAD cohorts, participants received GS-4182 200 mg or 400 mg (n=9 per cohort) or matched placebo (n=3 per cohort) QW for 6 weeks
- Intensive PK sampling was conducted through Day 7 for the SAD cohorts, and through 6 days post-dose for the Day 1 and Day 36 doses in the MAD cohorts; sparse PK sampling was performed throughout the study up to Day 77 (SAD cohorts) or Day 113 (MAD cohorts)
- A validated liquid chromatography with tandem mass spectrometry method was used to quantify plasma concentrations of GS-4182, LEN, and an additional metabolite
- Plasma PK parameters including AUC_{tau}, C_{max}, C_{trough}, t_{max}, and $t_{1/2}$, were estimated using Phoenix WinNonlin® software, using standard noncompartmental methods
- Incidences of adverse events and laboratory abnormalities were summarized using descriptive statistics

Results

Baseline Demographic Characteristics

- Across the two SAD and two MAD cohorts, a similar number of participants were assigned male or female at birth, with median age ranging from 25–35 years across cohorts (**Table 1**)
  - Overall, three participants were Asian, nine were Black or African American, and 22 were White

Table 1. Baseline Characteristics

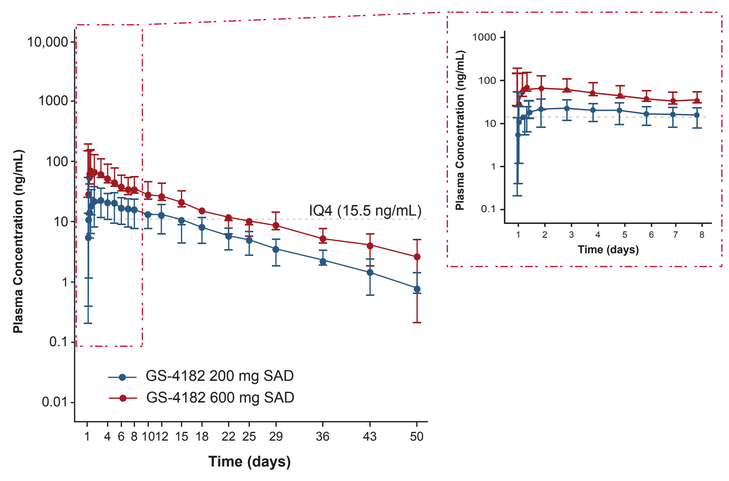
	SAD: GS-4182 200 mg (n=8)	SAD: GS-4182 600 mg (n=8)	MAD: GS-4182 200 mg QW (n=9)	MAD: GS-4182 400 mg QW (n=9)
Median (IQR) age, years	30 (26–39)	35 (28–42)	34 (32–39)	25 (24–27)
Sex at birth, male, n (%)	4 (50.0)	4 (50.0)	6 (66.7)	5 (55.6)
Race, n (%)				
Asian	0	2 (25.0)	1 (11.1)	0
Black or African America	3 (37.5)	1 (12.5)	3 (33.3)	2 (22.2)
White	5 (62.5)	5 (62.5)	5 (55.6)	7 (77.8)
Hispanic or Latinx ethnicity, n (%)	4 (50.0)	1 (12.5)	6 (66.7)	2 (22.2)
Mean (SD) BMI, kg/m^2	22.5 (2.9)	24.6 (1.3)	25.5 (2.4)	24.9 (2.4)

BMI, body mass index; MAD, multiple ascending dose; SAD, single ascending dose.

PK Results: SAD Cohorts

- Higher LEN relative bioavailability was observed for GS-4182 compared with historic data for direct oral LEN administration (19% and 15% for GS-4182 200 mg and 600 mg, respectively; 10% and 5% for LEN 300 mg and 600 mg, respectively)
- Mean LEN concentrations on Day 7 following single doses of GS-4182 200 mg or 600 mg were above IQ4 (efficacy target)[1,2] (**Figure 1**)

Figure 1. LEN Plasma Concentration-Time Profile Following Single, Oral Administration of GS-4182 200 mg (Blue) and 600 mg (Red)



Data presented as mean (SD). The dotted line represents IQ4.
IQ4, inhibitory quotient 4; LEN, lenacapavir; SAD, single ascending dose.

- LEN plasma PK parameters following single oral administration of GS-4182 are reported in **Table 2**
  - A dose-proportional increase in LEN exposure was observed for single doses of GS-4182 200 mg to 600 mg
  - Median LEN t_{max} was 1.0–2.0 days following GS-4182 200 mg or 600 mg administration, with a median $t_{1/2}$ of approximately 11 days
- Following administration of GS-4182, plasma concentrations of GS-4182 were undetectable for the majority of the samples in this study, with only 1.3% of samples above the lower limit of quantification
- Following single-dose administration of GS-4182 200 mg and 600 mg, metabolite Met-A was rapidly eliminated within 2–3 days and resulted in dose-proportional increase in exposure

Table 2. LEN Plasma PK Parameters Following Single, Oral Administration of GS-4182 200 mg and 600 mg

Geometric mean (%GCV)	SAD: GS-4182 200 mg (n=8)	SAD: GS-4182 600 mg (n=8)
C_{max}, ng/mL	22.1 (60.3)	61.7 (111.0)
AUC_{inf}, h•ng/mL	8120 (53.5)	18,500 (61.5)
AUC_{0-168}, h•ng/mL	2870 (58.3)	7050 (72.7)
t_{max}, days[a]	2.0 (1.0–3.0)	1.0 (0.3–4.0)
$t_{1/2}$, days[a]	11.0 (8.0–16.9)	11.6 (8.9–16.5)

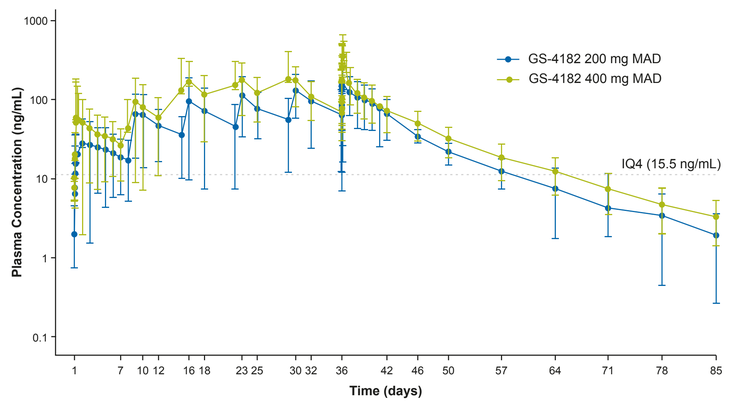
[a]Data shown as median (range).
%GCV, percentage geometric coefficient of variation; AUC_{0-168}, partial area under the concentration-time curve from 0 to 168 hours; AUC_{inf}, area under the concentration-time curve extrapolated to infinity; C_{max}, maximum concentration; LEN, lenacapavir; PK, pharmacokinetics; SAD, single ascending dose; $t_{1/2}$, half-life; t_{max}, time to maximum concentration.

PK Results: MAD Cohorts

- A dose-proportional increase in LEN exposure was observed following multiple QW doses of GS-4182 200 mg and 400 mg, with both doses maintaining mean LEN plasma concentrations above IQ4 throughout the 6-week period (**Figure 2**)
- Steady state was achieved by Day 36 (**Figure 2**)
- LEN plasma PK parameters following 6 weeks of GS-4182 200 mg and 400 mg QW dosing are reported in **Table 3**
- There was, approximately, 6–7-fold accumulation in C_{max}, 3-fold accumulation in C_{trough}, and 4-fold accumulation in AUC_{tau} after 6 weeks of QW dosing (**Table 3**)
- There was no accumulation of metabolite Met-A following 6 weeks of GS-4182 200 mg or 400 mg QW dosing

Results (cont.)

Figure 2. LEN Plasma Concentration-Time Profile Following Oral Administration of GS-4182 200 mg (Blue) and 400 mg (Green) QW for 6 Weeks



Data presented as mean (SD). The dotted line represents IQ4.
IQ4, inhibitory quotient 4; LEN, lenacapavir; MAD, multiple ascending dose; QW, once weekly.

Table 3. LEN Plasma PK Parameters Following Oral Administration of GS-4182 200 mg and 400 mg QW for 6 Weeks

	MAD: GS-4182 200 mg QW		MAD: GS-4182 400 mg QW	
Geometric mean (%GCV)	Week 1 (n=9)	Week 6 (n=9)	Week 1 (n=9)	Week 6 (n=9)
C_{max}, ng/mL	24.7 (68.8)	153 (76.7)	44.7 (141.0)	298 (124.0)
C_{trough}, ng/mL	14.9 (69.0)	51.7 (43.2)	21.1 (63.2)	60.4 (53.7)
AUC_{tau}, h•ng/mL	3150 (72.8)	14,100 (57.8)	4810 (85.1)	17,900 (65.2)
LEN accumulation, GLSM ratios (90% CI), Week 6/Week 1				
C_{max}, ng/mL	–	615 (374; 1010)	–	668 (291; 1530)
C_{trough}, ng/mL	–	340 (226; 512)	–	286 (190; 429)
AUC_{tau}, h•ng/mL	–	442 (281; 694)	–	372 (221; 625)

%GCV, percentage geometric coefficient of variation; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{max}, maximum concentration; C_{trough}, trough concentration; GLSM, geometric least-squares mean; LEN, lenacapavir; MAD, multiple ascending dose; PK, pharmacokinetics.

Safety

- The median (IQR) duration of follow-up was 180 (129–186) and 78 (78–78) days in the SAD 200 mg and 600 mg cohorts, respectively, and 113 (113–113) days in both the 200 mg and 400 mg QW MAD cohorts
- No Grade ≥3 treatment-emergent adverse events (TEAEs), serious TEAEs, or discontinuations of study drug due to TEAEs occurred, and no treatment-related TEAEs were Grade ≥2 (**Table 4**)
- Overall, Grade ≥3 treatment-emergent laboratory abnormalities were reported in nine participants and were transient, asymptomatic, and not clinically meaningful (**Table 4**)

Table 4. Safety Summary for SAD and MAD Cohorts

	SAD: GS-4182 200 mg (n=8)	SAD: GS-4182 600 mg (n=8)	MAD: GS-4182 200 mg QW (n=9)	MAD: GS-4182 400 mg QW (n=9)
TEAEs	3 (37.5)	0	0	4 (44.4)
Grade ≥3	0	0	0	0
Treatment-related TEAEs	3 (37.5)[a]	0	0	2 (22.2)[b]
Grade ≥2	0	0	0	0
Grade 3/4 laboratory abnormalities	3 (37.5)[c]	3 (37.5)[d]	2 (22.2)[e]	1 (11.1)[f]

n represents the number of participants; participants may have experienced ≥1 TEAE. [a]Diarrhea, n=2; lower abdominal pain, n=1; headache, n=1. [b]Dry eye, diarrhea, and vomiting, n=1 each. [c]Creatine kinase, n=3. [d]Direct bilirubin, fasting calculated LDL cholesterol, and fasting triglycerides, n=1 each. [e]Direct bilirubin, fasting calculated LDL cholesterol, and fasting cholesterol, n=1 each. [f]Fasting glucose, n=1.
LDL, low-density lipoprotein; MAD, multiple ascending dose; SAD, single ascending dose; TEAE, treatment-emergent adverse event.

References: 1. Sunlenca® (lenacapavir) US Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf (accessed July 2024). **2**. Sunlenca® (lenacapavir) Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf (accessed July 2024).
3. Subramanian R, et al. AIDS, Munich, Germany, July 22–26, 2024.

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