Effect of Acid-Reducing Agents on the Pharmacokinetics of Oral GS-4182

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Conclusions

- Lenacapavir (LEN) exposure following GS-4182 400 mg administration was similar with and without coadministration of esomeprazole (ESO)
- There were no new safety signals identified in the GS-4182 plus ESO drug-drug interaction (DDI) cohort
- Met-A exposure was similar between both cohorts
- GS-4182 can be administered without regard to acid-reducing agent use

Plain Language Summary

- GS-4182 is a new medicine that is being studied for the treatment of HIV infection
- GS-4182 is not yet approved for people with HIV
- GS-4182 is a 'prodrug' of an HIV medicine called lenacapavir
  - A prodrug is a tablet that is not active and must be broken down in the gut to become active; the active form of GS-4182 is called lenacapavir
- Drugs that lower the amount of acid in the stomach can sometimes change how well GS-4182 works
- In this study, we tested if GS-4182 would still work if given together with another drug called esomeprazole (used to lower stomach acid) in people who do not have HIV
  - Sometimes HIV medicines are tested in people without HIV to see how they are broken down by the body
- We found that giving GS-4182 with esomeprazole did not affect the function of GS-4182
- The study showed that GS-4182 can be given to people who also take esomeprazole
- We are planning more studies to see how effective GS-4182 is at treating HIV infection

Background

- People with HIV-1 (PWH) are typically treated with once-daily oral combination regimens[1]
- High adherence to daily oral therapy is required to reduce the risk of virologic failure, but this remains a challenge for many PWH[2]
  - There is, therefore, an unmet need for novel, long-acting oral antiretroviral therapies to help address suboptimal adherence and reduce HIV-1 treatment fatigue[3]
- LEN is a first-in-class HIV-1 capsid inhibitor currently approved for treating multidrug-resistant HIV-1 in heavily treatment-experienced PWH, in combination with other antiretrovirals[4,5]
- Although LEN exhibits a long half-life following oral administration (10–12 days), its absolute oral bioavailability is low (6–10%)[4,5]
- GS-4182 is an oral LEN prodrug that is metabolised in the gastrointestinal tract, releasing LEN and the metabolite Met-A[6]
  - GS-4182 has demonstrated potent anti-HIV-1 activity, alongside a pharmacokinetic (PK) and safety profile supportive of once-weekly dosing[7]
- Potential DDIs are important to consider due to the high rates of polypharmacy in PWH[8]
- Acid-reducing agents elevate gastric pH, which can alter the bioavailability of other concomitantly administered oral drugs, potentially resulting in reduced efficacy or increased adverse events[9]
- In this Phase 1a DDI analysis, we assessed the impact of an acid-reducing agent (ESO) on GS-4182 PK and safety

Objective

- To assess the impact of ESO on the PK and safety of oral GS-4182 in participants without HIV-1

Methods

- This Phase 1a study enrolled participants without HIV-1 aged 18–45 years into various GS-4182 single-dose, multiple-dose, food-effect, and DDI cohorts
- In this DDI analysis for ESO and GS-4182, we compared two cohorts:
  - ESO DDI open-label cohort in which participants received daily ESO 40 mg on Days 1–5, plus a single dose of GS-4182 400 mg on Day 5 under fasting conditions
  - Blinded, placebo-controlled, multiple-dose cohort in which participants received once-weekly GS-4182 400 mg administered without ESO under fasting conditions (referred to as the reference cohort)
- GS-4182 PK data from the ESO DDI cohort were compared with Week 1 PK data from the reference cohort
- Intensive PK sampling was conducted through 168 hours post-first dose in both cohorts
- Analysis included plasma PK parameters of LEN and Met-A with and without coadministration of ESO
  - Area under the concentration-time curve (AUC) from 0–168 hours ($AUC_{0–168}$) for LEN
  - AUC from dosing to the last measurable concentration (AUC_{last}) for Met-A
  - Maximum concentration (C_{max})
  - Time taken to reach maximum concentration (T_{max})
- Plasma PK parameters were estimated using Phoenix WinNonlin® Version 8.2 software, using standard noncompartmental methods
- Geometric-least squares means (GLSM) ratios and 90% CIs were calculated for LEN AUC_{0-168h}, AUC_{last}, C_{max}, and concentration at 168 hours (C_{168h})

Results

Participant Details

- In total, 12 participants were enrolled in the ESO DDI cohort and 12 participants were enrolled in the reference cohort (n=9 received GS-4182 and n=3 received placebo [data for participants receiving placebo are not reported here]) (**Table 1**)
  - Median age was 31 years in the DDI cohort and 25 years in the reference cohort

Table 1. Baseline Characteristics

	ESO DDI Cohort GS-4182 400 mg + ESO 40 mg (n=12)	Reference Cohort GS-4182 400 mg (n=9)
Median (IQR) age, years	31 (28–37)	25 (24–27)
Sex at birth, male, n (%)	9 (75.0)	5 (55.6)
Race, n (%)		
White	8 (66.7)	7 (77.8)
Black or African American	3 (25.0)	2 (22.2)
American Indian or Alaska Native	1 (8.3)	0
Ethnicity, n (%)		
Hispanic or Latinx	3 (25.0)	2 (22.2)
Mean (SD) BMI, kg/m²	23.9 (2.46)	24.9 (2.35)

Please note that data for participants receiving placebo are not shown.
BMI, body mass index; DDI, drug-drug interaction; ESO, esomeprazole; IQR, interquartile range.

LEN and Met-A Exposure With and Without ESO

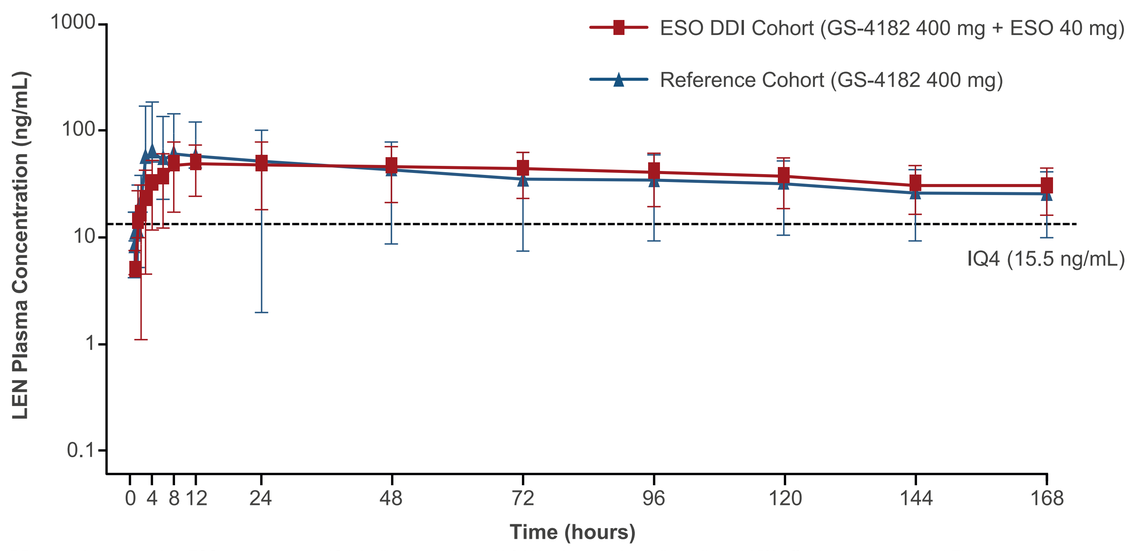
- Median time to LEN T_{max} was 12.0 hours in both the ESO DDI and reference cohorts (**Table 2**)
- GLSM ratios (90% CI) for plasma LEN and Met-A PK parameters are presented in **Table 2**
- LEN exposure was similar following GS-4182 administration, with and without ESO (**Figure 1**)
- Met-A exposure was also similar between both cohorts (**Figure 2**)

Table 2. LEN and Met-A Exposure With and Without ESO

	ESO DDI Cohort GS-4182 400 mg + ESO 40 mg (n=12)	Reference Cohort GS-4182 400 mg (n=9)	GLSM Ratio, % (90% CI)
LEN Plasma PK parameter			
Geometric mean $AUC_{0–168h}$ (%GCV), hr*ng/mL	6080 (45.1)	4810 (85.1)	126 (81.2; 197)
Geometric mean C_{max} (%GCV), ng/mL	50.7 (54.4)	44.7 (141.0)	113 (62.5; 206)
Geometric mean C_{168h} (%GCV), ng/mL	28.0 (40.6)	21.1 (63.2)	132 (91.9; 191)
Median T_{max} (IQR), hours	12.0 (10.0–48.0)	12.0 (4.0–24.1)	-
Met-A Plasma PK parameter			
Geometric mean AUC_{last} (%GCV), hr*ng/mL	466 (16.4)	416 (30.8)	112 (93.9; 134)
Geometric mean C_{max} (%GCV), ng/mL	204 (28.4)	161 (49.8)	126 (95.0; 167)
Median T_{max} (IQR), hours	2.00 (1.50–3.54)	2.00 (1.50–2.00)	-

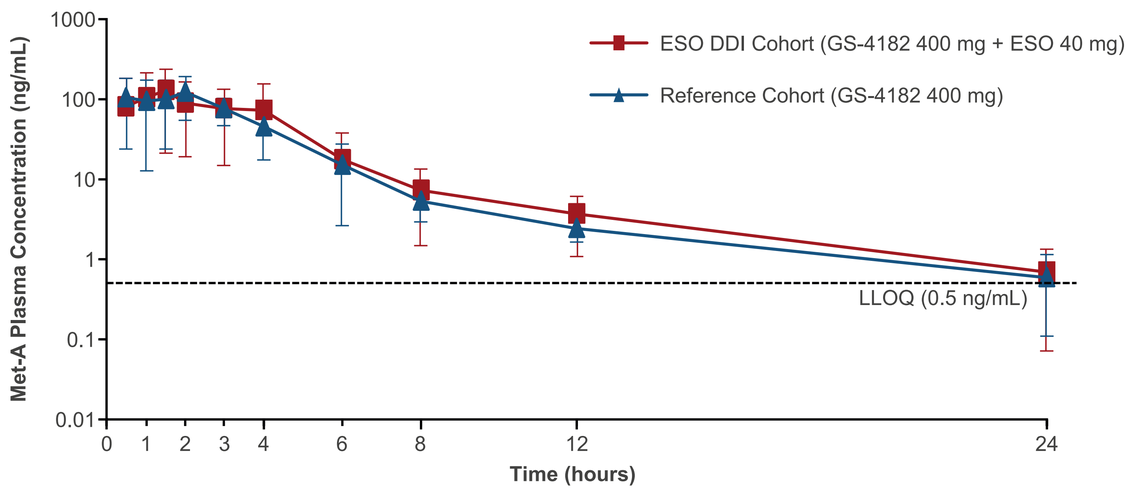
Please note that data for participants receiving placebo are not shown.
$AUC_{0–168}$, area under the concentration-time curve from 0–168 hours; AUC_{last}, area under the concentration-time curve from dosing to the last measurable concentration; C_{max}, maximum concentration; C_{168h}, concentration at 168 hours; DDI, drug-drug interaction; ESO, esomeprazole; GCV, geometric coefficient of variation; GLSM, geometric least squares mean; LEN, lenacapavir; PK, pharmacokinetics; T_{max}, time taken to reach maximum concentration.

Figure 1. Mean (SD) Plasma LEN Exposure With and Without ESO



DDI, drug-drug interaction; ESO, esomeprazole; IQ4, inhibitory quotient 4 (4-fold in-vitro protein binding-adjusted 95% effective concentration); LEN, lenacapavir.

Figure 2. Mean (SD) Plasma Met-A Exposure With and Without ESO[a]



[a]In both cohorts, Met-A plasma concentrations from 48 hours to 168 hours were below the limit of quantitation (LLOQ 0.5 ng/mL; indicated by the dashed line).
DDI, drug-drug interaction; ESO, esomeprazole; LEN, lenacapavir; LLOQ, lower limit of quantitation.

Safety

- There were no new safety signals observed in the ESO DDI cohort (**Table 3**)

Table 3. Adverse Events and Laboratory Abnormalities

Participants With Event, n (%)	ESO DDI Cohort GS-4182 400 mg + ESO 40 mg (n=12)	Reference Cohort GS-4182 400 mg (n=9)
Any Grade TEAE	6 (50.0)	4 (44.4)
Any Grade ≥3 TEAE	0	0
Any serious TEAE	0	0
Any study drug-related TEAE	3 (25.0)	2 (22.2)
Any Grade ≥2 study drug-related TEAE	0	0
Any serious study drug-related TEAE	0	0
Any TEAE leading to premature discontinuation of study drug	0	0
Any Grade ≥3 laboratory abnormalities	3 (25.0)	1 (11.1)

Please note that data for participants receiving placebo are not shown.
DDI, drug-drug interaction; ESO, esomeprazole; TEAE, treatment-emergent adverse event.

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