Antiviral Activity, Pharmacokinetics, and Safety of Oral GS-3242 for HIV-1 Treatment

Poster #P042

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Conclusions

- Oral GS-3242 demonstrated robust antiviral activity across all dose cohorts, with mean HIV-1 RNA reductions >2 $\log_{10}$ copies/mL from baseline to Day 11
- The pharmacokinetic profile of oral GS-3242 supports its potential as a long-acting oral antiretroviral
- Oral GS-3242 was well tolerated
- These findings support ongoing Phase 2 development of GS-3242 in combination with lenacapavir (NCT07645287) as an oral weekly HIV-1 treatment regimen in addition to as an injectable regimen (NCT07708727)

Plain Language Summary

- GS-3242 is a new medicine being studied for the treatment of HIV
  - Unlike most HIV medicines, GS-3242 may not need to be taken every day
  - GS-3242 stays in the body for a relatively long time after it is taken by mouth
- At the end of the study, GS-3242 lowered the amount of HIV in the blood at all doses tested (75 mg to 900 mg taken daily for 2 days)
- Researchers did not identify any major safety concerns with GS-3242, and no serious side effects were reported
  - No participants stopped taking GS-3242 because of side effects
- These results suggest that GS-3242 may be a treatment option for people who would prefer to take HIV treatment less often than every day

Background

- Regimens containing integrase strand transfer inhibitors (INSTIs) are the standard of care for HIV-1 treatment[1]
- Some people with HIV-1 may experience challenges adhering to daily oral antiretroviral therapy due to pill fatigue and stigma[2]
- Long-acting antiretrovirals for HIV-1 treatment, both injectable and oral, may help to address barriers to optimal adherence
- GS-3242 is an INSTI with potent anti-HIV-1 activity[3]
- As previously presented, pharmacokinetics data in humans indicate GS-3242 can be administered as a long-acting injectable, with a dosing interval of at least every 4 months[3]
- Here we present oral pharmacokinetics data in addition to updating antiviral activity data

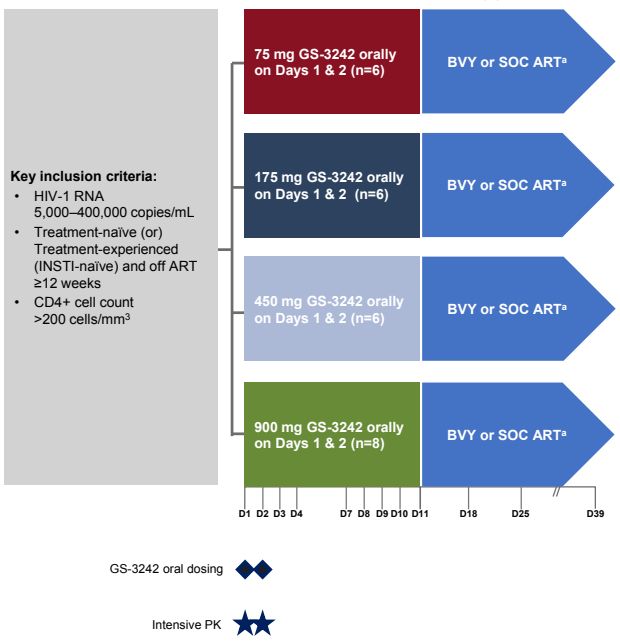
Objective

- To evaluate the antiviral activity, pharmacokinetics, pharmacokinetic–viral dynamic relationship, and safety of oral GS-3242 in a Phase 1b study

Methods

- This open-label, Phase 1b, multicentre study enrolled participants aged 18–65 years old with HIV-1 who were treatment naïve or INSTI naïve and had not received any antiretrovirals within 12 weeks prior to screening
  - Eligible participants had plasma HIV-1 RNA ≥5000–≤400,000 copies/mL and a CD4 cell count of >200cells/mm^3 at screening
- Participants received oral GS-3242 once daily on Days 1 and 2 (fasted) in four dose cohorts (75 mg, 175 mg, 450 mg, or 900 mg) (**Figure 1**)
- The primary endpoint was change in plasma HIV-1 RNA from baseline to Day 11
  - Secondary endpoints included the pharmacokinetics and pharmacokinetic–viral dynamic relationships of HIV-1 RNA, and safety of GS-3242
- Results were summarised using descriptive statistics

Figure 1: Phase 1b Study Design



[a]After assessments on Day 11 or upon early termination, participants initiated a regimen of BVY provided by the sponsor or alternative SOC ART regimen selected by the investigator.
ART, antiretroviral therapy; BVY, Biktarvy; D, Day; INSTI, integrase strand transfer inhibitor; PK, pharmacokinetics; SOC, standard of care.

Results

Participants

- A total of 26 participants (75 mg [n=6], 175 mg [n=6], 450 mg [n=6], and 900 mg [n=8]) were enrolled and dosed
- Median (range) age was 29 (18–65) years (**Table 1**)
- Overall, 84.6% of participants were male (**Table 1**)
- Mean (SD) HIV-1 RNA, $\log_{10}$ copies/mL was 4.77 (0.49) at baseline (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

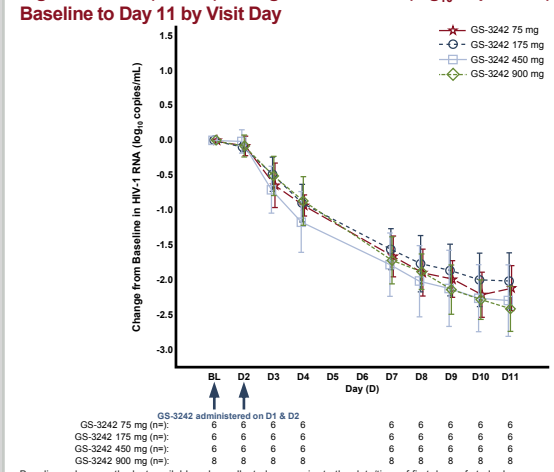
	75 mg (n=6)	175 mg (n=6)	450 mg (n=6)	900 mg (n=8)	Overall (N=26)
Median (range) age, years	32 (27–38)	28 (22–65)	36 (20–60)	29 (18–34)	29 (18–65)
Assigned male at birth, n (%)	5 (83.3)	5 (83.3)	6 (100)	6 (75.0)	22 (84.6)
Race, n (%)					
Asian	3 (50.0)	2 (33.3)	0	5 (62.5)	10 (38.5)
Black/African American	1 (16.7)	2 (33.3)	2 (33.3)	0	5 (19.2)
White	1 (16.7)	1 (16.7)	3 (50.0)	3 (37.5)	8 (30.8)
Other	1 (16.7)	1 (16.7)	1 (16.7)	0	3 (11.5)
Mean (SD) HIV-1 RNA at baseline, $\log_{10}$ copies/mL	4.45 (0.48)	4.80 (0.54)	4.90 (0.49)	4.88 (0.43)	4.77 (0.49)
Median (range) weight, kg	66.2 (56.4–89.0)	62.0 (50.1–105.3)	70.1 (61.9–92.2)	66.8 (44.8–92.2)	65.7 (44.8–105.3)
Median (range) BMI, kg/m^2	22.8 (20.3–32.7)	20.9 (16.7–42.4)	21.6 (20.0–28.1)	23.4 (15.2–36.0)	22.2 (15.2–42.4)

BMI, body mass index.

Efficacy

- Mean (95% CI) changes in HIV-1 RNA ($\log_{10}$ copies/mL) from baseline to Day 11 were (**Figure 2**):
  - 75 mg: –2.11 (–2.45; –1.78)
  - 175 mg: –2.01 (–2.44; –1.59)
  - 450 mg: –2.29 (–2.83; –1.76)
  - 900 mg: –2.41 (–2.68; –2.14)

Figure 2. Mean (95% CI) Change in HIV-1 RNA ($\log_{10}$ copies/mL) from Baseline to Day 11 by Visit Day



Baseline value was the last available value collected on or prior to the date/time of first dose of study drug.
No data were collected on Day 5 or Day 6.
BL, baseline; D, Day.

Pharmacokinetics

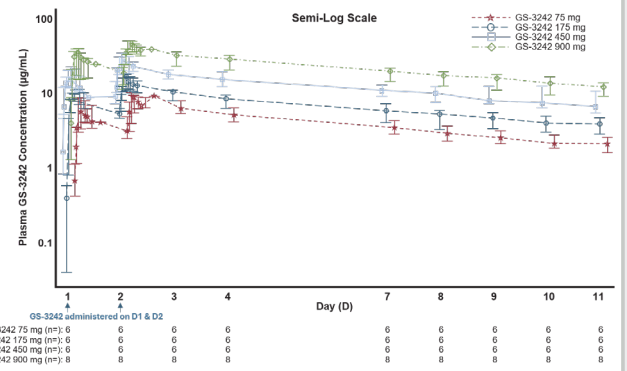
- Mean (SD) GS-3242 concentrations (µg/mL) on Day 11 were (**Figure 3**)[a]:
  - 75 mg: 1.71 (0.72) > inhibitory quotient (IQ) 1
  - 175 mg: 3.37 (1.62) >IQ3
  - 450 mg: 6.48 (2.49) >IQ5
  - 900 mg: 10.2 (3.12) >IQ10
- Median terminal half-lives of GS-3242 are in **Table 2**

Table 2. Median Terminal Half-lives of GS-3242

Dose cohort	Median terminal half-life (Days)
75 mg	5.59
175 mg	5.62
450 mg	6.47
900 mg	5.99

[a]IQ is defined as the ratio of GS-3242 plasma concentration at Day 11 to the protein-adjusted effective concentration to achieve 95% inhibition. IQ1 = 0.957 ug/mL; IQ3 = 2.872 ug/mL; IQ5 = 4.787 ug/mL; IQ10 = 9.574 ug/mL.

Figure 3. Mean (SD) Plasma GS-3242 Concentration versus Time up to Day 11

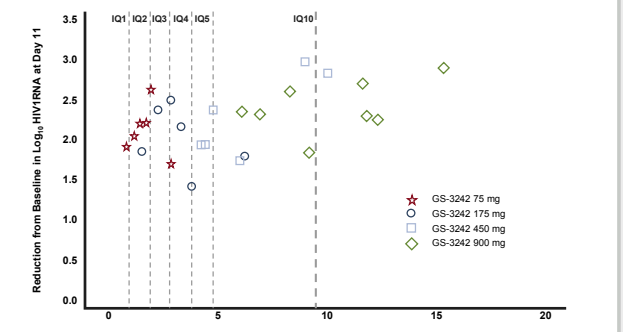


No data were collected on Day 5 or Day 6. Pharmacokinetic data were available from only one participant per cohort at the Day 1 12-hour time point in the 75 mg, 450 mg, and 900 mg cohorts, and the Day 2 12-hour time point in the 75 mg and 900 mg cohorts. Data points for each dose are staggered for visual clarity and do not represent different timepoints.
D, Day.

Pharmacokinetic–Viral Dynamic Relationship

- Across the entire individual exposure range at Day 11 (from 0.88- to 16.0-fold higher than the protein-adjusted EC_{95} of 0.957 µg/mL), robust anti-viral activities were observed (**Figure 4**)

Figure 4. Relationship between Reduction from Baseline in HIV-1 RNA ($\log_{10}$ copies/mL) and GS-3242 Concentration on Day 11



IQ is defined as the ratio of GS-3242 plasma concentration at Day 11 to the protein-adjusted effective concentration to achieve 95% inhibition. IQ1 = 0.957 ug/mL; IQ2 = 1.915 ug/mL; IQ3 = 2.872 ug/mL; IQ4 = 3.830 ug/mL; IQ5 = 4.787 ug/mL; IQ10 = 9.574 ug/mL.
IQ, inhibitory quotient.

Safety

- AEs occurring in ≥2 participant included headache (n=4), constipation (n=2) and dizziness (n=2)
- No serious AEs or AEs leading to premature discontinuation of study drug occurred (**Table 3**)
- All treatment-related adverse events were Grade 1, and no dose-response relationships were observed
- None of the laboratory abnormalities were clinically significant

Table 3. Safety Overview

n (%)	75 mg (n=6)	175 mg (n=6)	450 mg (n=6)	900 mg (n=8)
Any AE	3 (50.0)	3 (50.0)	3 (50.0)	3 (37.5)
Grade 2	1 (16.7)	0	1 (16.7)	1 (12.5)
Grade ≥3	0	1 (16.7)[a]	0	0
AE related to study drug	2 (33.3)[b]	1 (16.7)[c]	0	0
Grade ≥2	0	0	0	0
Serious AE	0	0	0	0
AE leading to premature discontinuation of study drug	0	0	0	0
Grade 4 laboratory abnormalities	0	0	1 (16.7)[d]	1 (12.5)[e]

[a]Grade 3 neutropenia that was asymptomatic and not clinically significant. [b]Grade 1 nightmare and Grade 1 poor quality sleep; Grade 1 rash erythematous. [c]Grade 1 dizziness. [d]Lipase increased. [e]Creatine kinase increased.
AE, adverse event.

References:
1. Zhao AV, et al. *Retrovirology*. 2022;19:22.
2. Claborn KR, et al. *Psychol Health Med*. 2015; 20:255–65.
3. Gupta S, et al. CROI 2026; Presentation 174.

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