Nonclinical Pharmacokinetics of a Novel INSTI GS-3242 Supports a Human Long-Acting Injectable

Poster #490

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Conclusions

- GS-3242 is predicted to have low in-vivo clearance (CL) and low volume of distribution at steady state (V_{ss}) in humans
- GS-3242 is expected to exhibit slow, depot rate release-governed, long-acting injectable (LAI) pharmacokinetics (PK)
- GS-3242 is predicted to maintain efficacious plasma concentrations with dosing intervals of at least once every 4 months (Q4M) in humans
- The nonclinical absorption, distribution, metabolism, and excretion (ADME) properties support the development of GS-3242 as a novel integrase strand transfer inhibitor (INSTI) with potential to enable LAI administration for the treatment of HIV-1
- Phase 1 studies evaluating the safety, PK and antiviral activity of GS-3242 are ongoing; the clinical PK of GS-3242 will be described in a complementary oral presentation (CROI Oral 174)[1]

Plain Language Summary

- GS-3242 is a new medicine being tested to treat HIV. Unlike most other HIV medicines that are taken as daily pills, GS-3242 can be given as an injection that may last for several months
- We designed a molecule that lasts for a long time in animals, and did studies in animals to see how long GS-3242 remained in the blood at high enough levels after an injection
- We found that GS-3242 stayed in the blood for enough time and predict that it can be given as an injection every 4 months or longer in humans

References: **1.** Gupta S, et al. CROI 2026: Oral 174. **2.** Zhao AV, et al. *Retrovirology*. 2022;19:22. **3.** Claborn KR, et al. *Psychol Health Med*. 2015; 20:255–65. **4.** Hansen D, et al. CROI 2026. Poster 521.

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Background

- INSTI-containing regimens are the cornerstone of treatment for HIV-1[2]
- Long-acting antiretroviral therapies may offer advantages over daily oral treatments for some people with HIV-1, including improved adherence and reduced treatment burden[3]
- GS-3242 is a novel, investigational INSTI which has shown potent preclinical anti-HIV-1 activity[4]
- GS-3242 has physiochemical properties well suited for a LAI formulation
- The safety, PK, and antiviral activity of GS-3242 are being investigated in Phase 1a and Phase 1b studies[1]
- Characterizing the nonclinical ADME properties of GS-3242 is critical to understanding its long-acting PK profile and supporting clinical dose selection

Objective

- Success in long-acting PK is governed by minimizing CL, maximizing potency, and optimizing depot release rate and amount (the pharmacological properties of GS-3242 are described in CROI Poster 521[4])
- This poster describes elucidation of the ADME properties of GS-3242, including CL and depot characteristics

Methods

- GS-3242 metabolic stability and protein binding were assessed in nonclinical and human liver microsomes and plasma, respectively
- Intravenous (IV) PK studies were conducted in rat, dog, and monkey
- Long-acting subcutaneous (SC) and intramuscular (IM) PK studies with an aqueous LAI suspension formulation were conducted in cynomolgus monkey
- Human systemic CL was estimated from in-vitro-predicted CL and adjusted for the in-vitro to in-vivo disconnect observed in animals
- The human V_{ss} was predicted from nonclinical species
- Clinical PK was predicted using the scaled metabolic CL and depot release rates observed in monkey
- Monkey LAI PK was deconvoluted using inbuilt Phoenix WinNonlin modules, Version 6.4 (Pharsight Corporation, Mountain View, CA)

Results

Metabolic Stability and Plasma Protein Binding

- GS-3242 had low predicted CL across species (**Table 1**)
- GS-3242 was highly plasma protein bound, suggesting:
  - In-vivo CL will be significantly lower than in-vitro CL
  - GS-3242 will predominantly be restricted to the plasma and extracellular fluids

Results (Cont.)

Table 1. Metabolic Stability and Plasma Protein Binding of GS-3242 in Rat, Dog, Monkey, and Human

	Plasma-Free Fraction, %	^{3}H-Predicted CL, L/h/kg	Predicted Hepatic Extraction, %
SD Rat	<0.01	0.355	8
Beagle Dog	0.06	0.260	14
Cynomolgus Monkey	0.04	0.285	18
Rhesus Monkey	0.05	0.395	15
Human	0.03	0.080	6

CL, clearance; SD, Sprague-Dawley.

IV PK of GS-3242

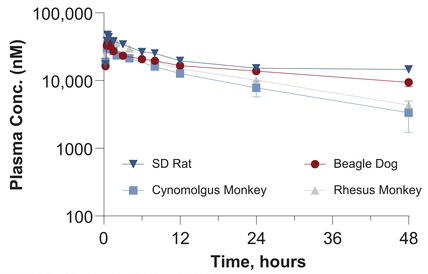
- GS-3242 had very low in-vivo CL, with hepatic extraction ratios <0.2% (**Table 2**)
- Consistent with the high plasma protein binding of GS-3242:
  - In-vitro CL values over-predicted in-vivo CL by >100-fold
  - GS-3242 had low volumes of distribution (<0.2 L/kg)
- Plasma concentration-time profiles of GS-3242 PK following IV administration across species are shown in **Figure 1**

Table 2. IV PK of GS-3242 Across Animal Species

Species	SD Rat	Beagle Dog	Cynomolgus Monkey	Rhesus Monkey
Dose, mg/kg	1.0	1.0	1.0	1.0
$t_{1/2}$, days	>20	>1.5	>1	Approx. 1
Hepatic Extraction Ratio, %	<0.2	<0.2	<0.2	<0.2
V_{ss}, L/kg	<0.2	<0.1	<0.1	<0.1

Approx., approximately; IV, intravenous; PK, pharmacokinetics; SD, Sprague-Dawley; $t_{1/2}$, half-life; V_{ss}, volume of distribution at steady state.

Figure 1: GS-3242 PK Following IV Administration in Rat, Dog, and Monkey



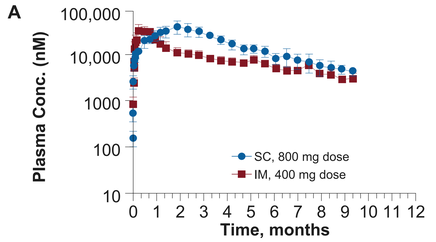
Conc., concentration; IV, intravenous; PK, pharmacokinetics; SD, Sprague-Dawley.

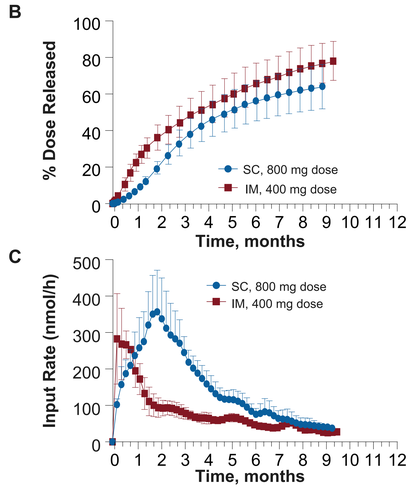
Long-Acting IM and SC Injectable PK of GS-3242 in Cynomolgus Monkey

- GS-3242 showed slow depot release (**Figure 2**), consistent with flip-flop kinetics in cynomolgus monkey SC and IM PK studies
- High plasma exposures were seen even up to 9 months after dosing
- The half-life ranged from 73 to 96 days, consistent with Q4M dosing or longer
- Fraction release was >64% over the collection period, suggesting slow and consistent release of the compound from the depot
- Fast release in the first 14 days represented <10% and <2% of dose for the IM and SC routes, respectively (**Figure 2**)

Figure 2: Long-Acting Plasma PK (A), Percentage of Dose Released (B), and Rate of Dose Release (C) of GS-3242 in Cynomolgus Monkey

Dose, mg	Route	% Dose Released[a]	Release Rate, h^{-1}	$t_{1/2}$, days
800	SC	64	0.0004	73
400	IM	78	0.0003	96





[a]% dose released at last PK time point.
Conc., concentration; h, hour; IM, intramuscular; PK, pharmacokinetic; SC, subcutaneous; $t_{1/2}$, half-life.

Human Dose Predictions

Table 3: Human Dose Predictions

	Methodology	Value
CL, L/h/kg	In-vitro predicted CL × average of in-vitro/in-vivo observed CL in animals	<0.001
V_{ss}, L/kg	Average of V_{ss} in animals	<0.1
Fraction Released, %	Assume complete release (based on monkey long-acting injectable pharmacokinetics)	100
Release Rate, h^{-1}	Based on cynomolgus monkey relative rate constant	<0.0004
Dose Q4M, g	Modelled using above parameters	<2

CL, clearance; h, hours; Q4M, once every 4 months; V_{ss}, volume of distribution at steady state.

- The Q4M+ clinical dose is achievable via parenteral administration (**Table 3**)
- The human dose is projected to cover at a trough concentration five times the protein-adjusted 95% effective concentration (protein-adjusted 95% effective concentration = 957 ng/mL)