Nonclinical Profile of GS-4182, a Once-Weekly Oral Prodrug of the HIV-1 Capsid Inhibitor Lenacapavir in Clinical Development

Poster # WEPEA03

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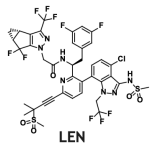
Conclusions

- GS-4182 is a novel solubilizing oral prodrug designed to liberate LEN in the gastrointestinal tract
- As designed, GS-4182 exhibits greater intestinal LEN absorption and improved systemic LEN exposure compared with oral administration of LEN in all nonclinical species tested
- GS-4182 reduced tablet size may lower pill burden when dosed as a single agent or fixed-dose combination with a partner agent
- GS-4182 exhibits a favorable nonclinical profile that supports its continued clinical development as a component of an optimized once-weekly oral regimen for the treatment of HIV-1 infection

GS-4182 clinical data is presented in Poster WEPEB117:
Shaik *et al*. Safety and Pharmacokinetic Profile of Single and Multiple Ascending Doses of GS-4182, an Oral Prodrug of Lenacapavir, in Participants without HIV-1.

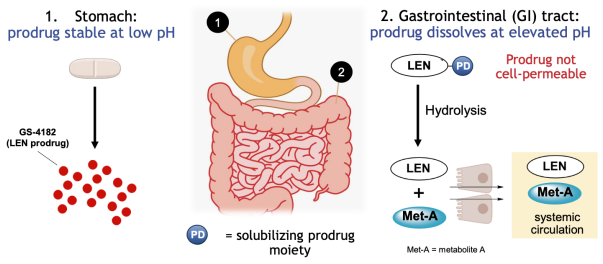
Introduction

- Current oral antiretroviral regimens for HIV-1 treatment require daily dosing, and high adherence is necessary to minimize the risk of emergent drug resistance.[1] Thus, there is a need for novel long-acting (LA) regimens to reduce the risk of non-adherence and treatment failure[2]
- Lenacapavir (LEN) properties optimal for LA injectable agent
  - Highly potent antiviral activity; EC_{50} = 105 pM ($paEC_{95}$ = 4 nM)[3]
  - Low human clearance of 0.06 L/h/kg[4]
  - Human *in vivo* $T_{1/2}$ ~ 12 days[4]
  - Low aqueous solubility at pH 2 and 7, <1 µg/mL[5]


LEN

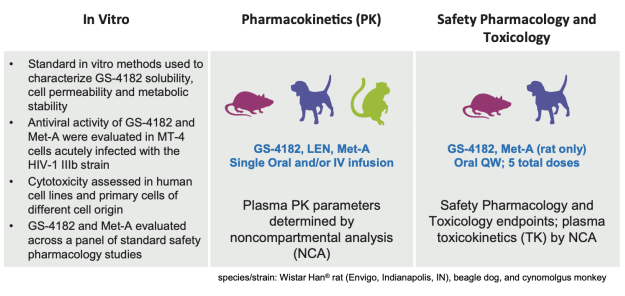
- LEN as a LA injectable formulation administered twice-yearly is approved for people with multidrug-resistant HIV-1 infection (Sunlenca®) and is being studied for use both in treatment-naive people with HIV (PWH) in combination with other antiretroviral agents and as a single subcutaneous injectable pre-exposure prophylaxis agent for HIV prevention
- LEN undergoes rapid absorption following oral administration, with a time to maximum concentration of 4 hours following 300 mg administration. However, the absolute oral bioavailability of LEN is low, at 6–10% [6,7]
- While LEN tablets support oral lead-in and bridging therapy in the clinic, LEN's solubility profile indicates some limitations in its oral absorption and tablet drug load that may present challenges for long-acting oral administration
- Herein, we describe the nonclinical profile of GS-4182, a novel solubilizing oral prodrug of LEN designed to reduce tablet size and pill burden when combined with a partner agent in a once-weekly (QW) oral treatment regimen

Figure 1. GS-4182 is a Novel Solubilizing Oral LEN Prodrug



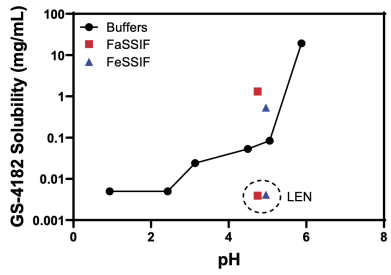
Methods

Figure 2. Methods



Results

Figure 3. Crystalline GS-4182 Shows Improved Solubility Compared to LEN



FaSSIF = Fasted State Simulated Intestinal Fluid, pH 6.5
FeSSIF = Fed State Simulated Intestinal Fluid, pH 5

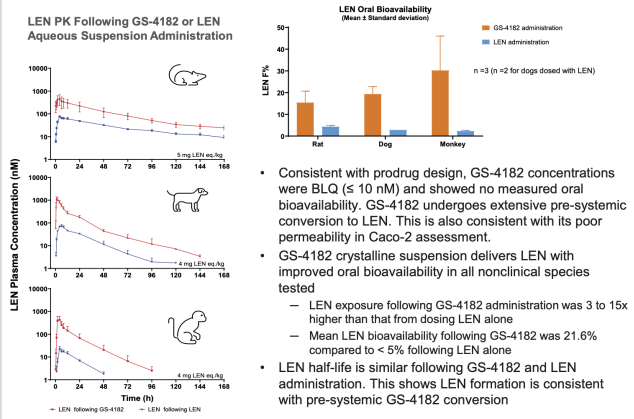
Table 1. GS-4182 Readily Converts to LEN in Human Gastrointestinal S9 Fractions

GS-4182 Property	Condition	Values
Permeability (AB/BA, 10^{-6} cm/s)	Caco-2 Cell Monolayer	<0.09/<0.09
GI S9 Stability ($t_{1/2}$, min)	Rat/Dog/Monkey/Human	122/99.4/19.7/96.1

Caco-2: human colon carcinoma cell line; GI S9: gastrointestinal S9 fraction

- GS-4182 shows poor permeability across Caco-2 monolayers

Figure 4. GS-4182 Shows Improved LEN Oral Bioavailability in Nonclinical PK



- Consistent with prodrug design, GS-4182 concentrations were BLQ (≤ 10 nM) and showed no measured oral bioavailability. GS-4182 undergoes extensive pre-systemic conversion to LEN. This is also consistent with its poor permeability in Caco-2 assessment.
- GS-4182 crystalline suspension delivers LEN with improved oral bioavailability in all nonclinical species tested
  - LEN exposure following GS-4182 administration was 3 to 15x higher than that from dosing LEN alone
  - Mean LEN bioavailability following GS-4182 was 21.6% compared to < 5% following LEN alone
- LEN half-life is similar following GS-4182 and LEN administration. This shows LEN formation is consistent with pre-systemic GS-4182 conversion

BLQ = below limit of quantitation

Table 2. Administration of GS-4182 and LEN Tablets in Dogs Upholds Superior Oral Bioavailability with GS-4182

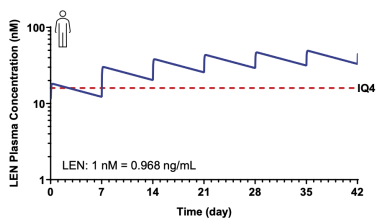
API	Formulation	API Form	Dose (mg-fixed)	LEN F %[a]
GS-4182	Non-Precipitating Solution	NA	55	17.2 ± 3.5
	Tablet	crystalline	100	14.5 ± 5.9
LEN	SDD Tablet	amorphous	40	4.6 ± 1

a. Values are mean ± standard deviation (n = 6)

- The 3-fold higher LEN oral bioavailability from GS-4182, allows for a reduced tablet size and lower pill burden if dosed as a single agent or fixed-dose combination with a partner agent

API = active pharmaceutical ingredient; NA = not applicable; SDD = spray dried dispersion

Figure 5. Predicted Human LEN PK with Oral GS-4182 QW Regimen



LEN Predicted PK	
GS-4182 dose	200 mg
LEN F (assumed)	20 %
LEN CL (L/h/kg)[5]	0.059 L/h/kg
LEN V_{SS} (L/kg)[5]	24 L/kg
k_a (assumed)	1 h^{-1}
C_{max} at steady-state	51 nM
C_{trough} at steady-state	33 nM
AUC_{0-168h} at steady-state	7100 nM•h

AUC = area under the PK curve; CL = clearance; C_{max} = maximum concentration; C_{trough} = concentration at the end of dose interval; F = oral bioavailability; k_a = oral absorption rate constant; PK = pharmacokinetic(s); V_{SS} = volume of distribution at steady state; IQ4 = 4 × plasma protein binding adjusted effective concentration for 95% inhibition in MT-4 cell Line

Nonclinical Safety Pharmacology Summary

In Vitro Receptor Binding Potencies

GS-4182 showed low potential for off-target effects against a panel of 87 molecular targets. Weak inhibition of radioligand binding were seen to 4 targets (IC_{50} range 1.1 - 4.1 µM) which are unlikely to be clinically relevant

In Vitro Cardiovascular System

GS-4182 (3-10 µM) showed no statistically significant inhibition of the hERG channel when compared to vehicle control values

In Vivo Central Nervous, Respiratory and Cardiovascular Systems

No GS-4182-related effects observed on the CNS or respiratory system in rats at oral doses up to 1000 mg/kg or the cardiovascular system in dogs at oral doses up to 100 mg/kg, the highest doses tested in these studies

Nonclinical Toxicology Summary

Genotoxicity

- GS-4182 and Met-A were both nongenotoxic in vitro and in nonclinical species

Repeat-Dose Toxicity

- No GS-4182-related target organ toxicity or systemic adversity identified in rats or dogs when administered once-weekly via oral gavage for 4 weeks (5 total doses)
- GS-4182 no-observed-adverse-effect levels (NOAEL) were the highest doses tested (1,000 mg/kg/week in rat; 100 mg/kg/week in dog)
- Margin of exposure of LEN at the NOAEL in rats and dogs is approximately 26- and 65-fold higher, respectively following QW dose of 200 mg GS-4182

Met-A Profile

- Met-A, a prodrug metabolite (Figure 1) is observed in systemic circulation following GS-4182 oral administration in nonclinical species and appears unlikely to have significant biological effects based on the following data:
  - Human predicted plasma half-life ($t_{1/2}$ ~6 h) is ~46-fold shorter than LEN $t_{1/2}$ (~12 d)
  - Projected human exposure is small relative to LEN and is not expected to accumulate
  - Met-A shows no antiviral activity in vitro: MT-4/HIV-1_{IIIb} EC_{50} > 50 µM
  - Met-A shows low in vitro cytotoxicity across multiple cell types: CC_{50} > 44 µM
  - Met-A shows no hits in the off-target panel (87 targets)
  - Met-A is not genotoxic and showed no hERG inhibition
  - In a repeat dose tox study in rats (once weekly oral dosing for 4 weeks), no Met-A-related target organ toxicity or systemic adversity was identified
  - The no-observed-effect level (NOEL) for Met-A was the highest dose tested (1,000 mg/kg/week) with an exposure margin of >24,000-fold compared to Met-A levels following a QW dose of 200 mg GS-4182

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