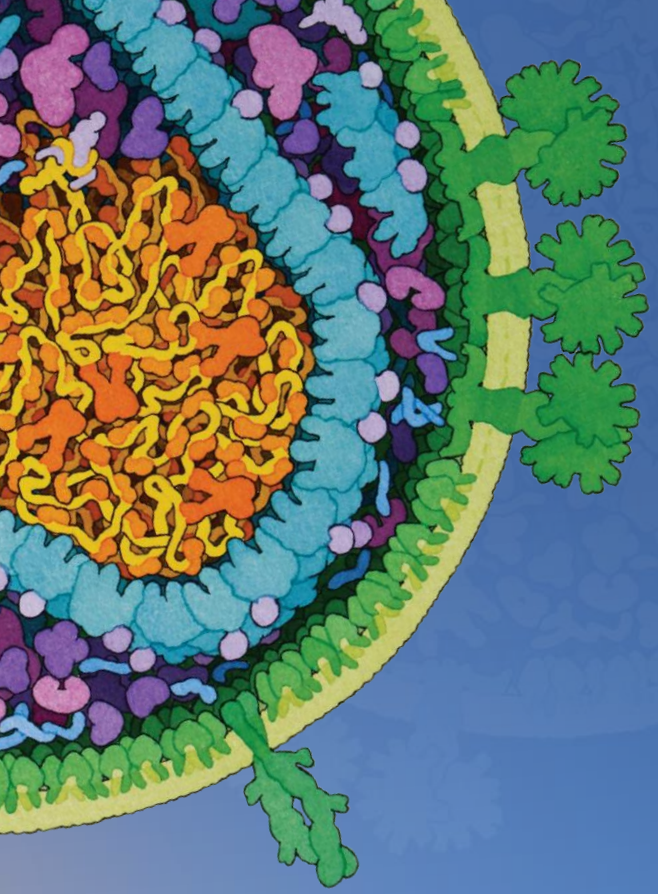

SCIENCE SPOTLIGHT™

PHARMACOKINETICS OF LENACAPAVIR, AN HIV-1 CAPSID INHIBITOR, IN HEPATIC IMPAIRMENT

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Disclosure: Employee of Gilead Sciences, Inc.

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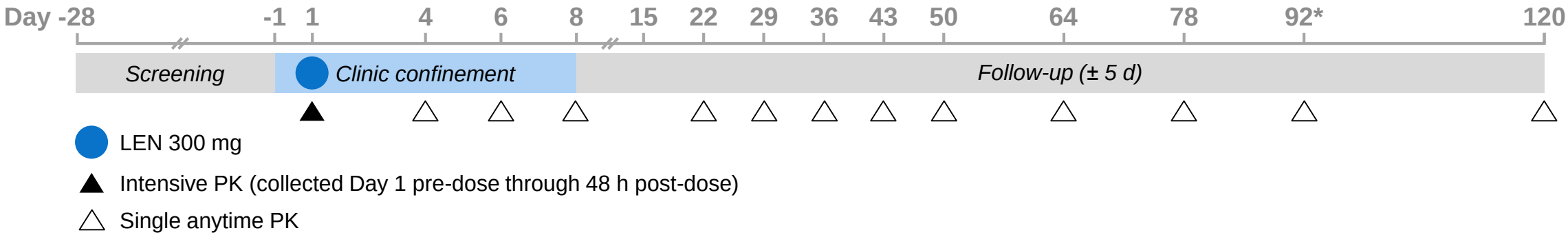
Introduction

- Lenacapavir (LEN; GS-6207), a potent, selective, first-in-class, multistage inhibitor of HIV-1 capsid function is in clinical development as a long-acting agent to treat HIV-1 infection, supporting weekly (oral LEN) or less frequent (subcutaneous LEN) dosing
- In people with HIV, LEN has shown potent antiviral activity and is well tolerated
- Clinical data indicate that LEN is a substrate for UGT1A1, P-glycoprotein, with a minor contribution from CYP3A
- LEN is predominantly excreted unchanged in feces (54%), with <1% in urine
- This study was conducted to evaluate the effect of moderate hepatic impairment (HI) on the pharmacokinetics (PK) of oral LEN to inform dosing recommendations in patients with mild and moderate HI

UGT1A1, uridine diphospho glucuronosyltransferase family 1A1

US DHHS FDA CDER; CBER. Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. May, 2003.

Methods: Study Design



- Phase 1, multi-center, open-label, single-dose, parallel-group study

Participants

- Ten participants with moderate HI (Child-Pugh-Turcotte B) and ten healthy controls with normal hepatic function (HC) were enrolled
- Healthy controls with normal hepatic function were matched to participants with moderate HI based on age (±10 y), sex, race and BMI (±15%)

Treatment

- Participants received a single oral dose of LEN 300 mg

*PK was collected through Day 92 post-dose

Demographics and Baseline Characteristics

	Moderate HI n=10	HC n=10
Median age, y (range)	56 (39–71)	55 (31–69)
Sex at birth, n (%)		
Male	7 (70)	7 (70)
Female	3 (30)	3 (30)
White race, n (%)	10 (100)	10 (100)
Median BMI, kg/m^2 (range)	32 (24–38)	30 (25–36)
Median CL_{cr}, mL/min (range)	113 (69–225)	117 (90–193)
CPT score, n (%)		
7	7 (70)	—
8	3 (30)	—

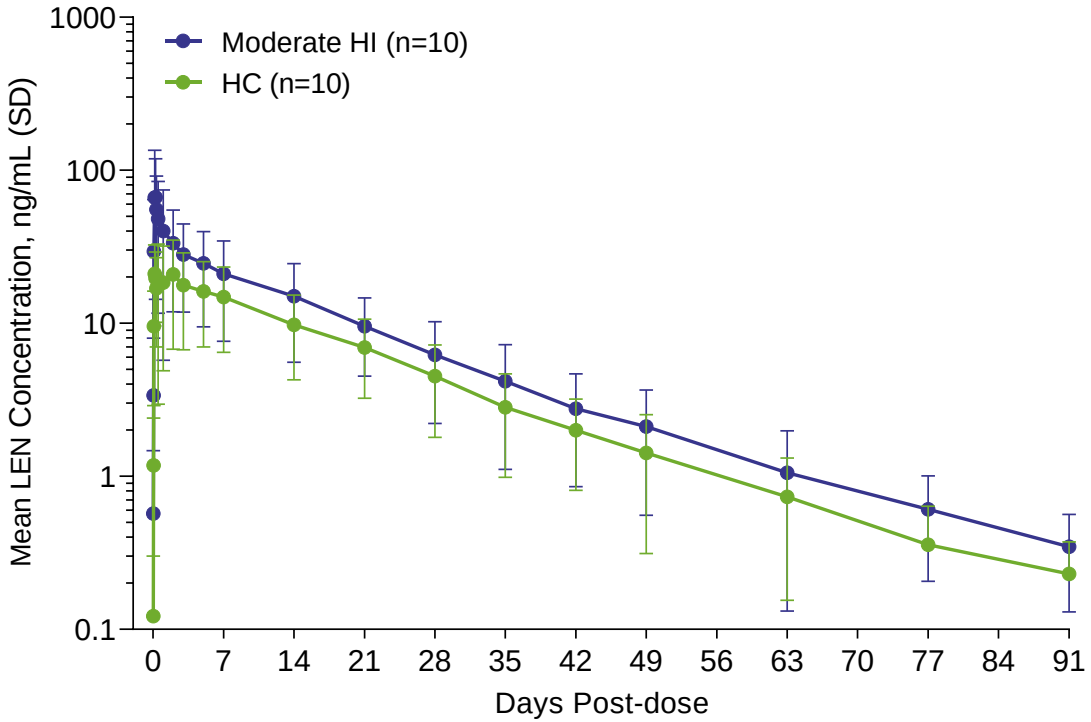
CL_{cr}, creatinine clearance by Cockcroft-Gault formula

Safety

- LEN was generally safe and well tolerated
- There were no serious or Grade 3 or 4 treatment emergent adverse events
- Laboratory abnormalities:
  - 4 participants with HI and 1 HC experienced Grade 3 or 4 lab abnormalities*, none of which were considered clinically relevant
  - All Grade 3 or 4 laboratory abnormalities improved on the next visit and/or were preexisting
- There were no clinically significant changes in vital signs or electrocardiograms

*HI: Grade 3 decreased calcium, sodium, platelet count, eGFR and increased serum glucose, urine glucose, total bilirubin. Grade 4 decreased lymphocytes; HC: Grade 4 increased creatinine kinase

LEN PK in Participants with Moderate Hepatic Impairment and Normal Hepatic Function



Parameter	Moderate HI n=10	HC n=10	%GLSM Ratio (90% CI)
AUC_{inf}, h·ng/mL	14,200 (62.6)	9,220 (53.2)	147 (94.7, 227)
C_{max}, ng/mL	82.7 (82.1)	26.8 (55.1)	261 (151, 452)
T_{max}, h	6.00 (4.00, 8.00)	4.00 (4.00, 5.97)	
$t_{1/2}$, h [d]	303 (251, 366) [12.6]	314 (284, 362) [13.1]	
Plasma protein binding, %	99.6 (0.194)	99.8 (0.145)	

PK parameters presented to 3 significant figures as mean (% coefficient of variation) except T_{max} (time to maximal concentration) and $t_{1/2}$ (half-life) which are presented as median (Q1, Q3). AUC_{inf}, AUC from time 0 to infinity; GLSM, geometric least squares mean; CI, confidence interval; SD, standard deviation

- Exploratory analyses indicated no significant relationships between LEN exposure (AUC and C_{max}) and CPT score or individual elements of CPT classification (albumin, total bilirubin, prothrombin time and INR)
- Based on cumulative safety data in the LEN SC and oral clinical program, no dose adjustment of LEN is recommended in patients with mild to moderate hepatic impairment

Conclusion

- LEN AUC and C_{max} were 1.5- and 2.6-fold higher, respectively, in participants with moderate hepatic impairment compared to their matched healthy controls
- Based on cumulative safety data in the LEN SC and oral clinical program, no dose adjustment of LEN is recommended in patients with mild to moderate hepatic impairment

Acknowledgments

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