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

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Disclosure: Employee of Gilead Sciences, Inc.
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 dosing (subcutaneous LEN).

- In people living with HIV, LEN has shown potent antiviral activity and is well tolerated.

- Clinical data indicate that LEN is a substrate for P-glycoprotein and UGT1A1; LEN is predominantly excreted unchanged in feces (54%), with minimal excretion in urine (<1%).

- This study was conducted to evaluate the effect of moderate HI on the PK of oral LEN to inform dosing recommendations in people with mild and moderate HI.

- **Primary Objective:** to evaluate the single-dose PK of LEN in volunteers with moderate HI and their matched HC.

- **Secondary Objective:** to evaluate the safety and tolerability of LEN single dose administration in volunteers with moderate HI and their matched HC.

HC, healthy controls; HI, hepatic impairment; PK, pharmacokinetics; UGT1A1, uridine diphospho-glucuronosyltransferase family 1A1.

Methods: Study Design

**Assessments**
- Plasma PK was collected through Day 92 post dose
- Plasma concentrations of LEN were measured by validated LC-MS/MS methods
- Equilibrium dialysis was used to determine LEN plasma protein binding at predose
- Safety was monitored throughout the study
- PK parameters were estimated using noncompartmental methods†
- A parametric analysis of variance model appropriate for a parallel design was fitted to logarithmically transformed PK parameters (AUC and $C_{\text{max}}$)
  - 90% CIs were constructed for the GLSM ratios of these parameters between HI group and matched HC

**Volunteers**
- Ten volunteers with moderate HI (CPT B) and 10 matched HC were enrolled
- Healthy volunteers with normal hepatic function were matched to volunteers with HI based on age ($\pm$10 y), sex, race and BMI ($\pm$15%)

**Treatment**
- Volunteers received a single oral dose of LEN 300 mg

*Based on review of preliminary LEN PK data, PK collections may be discontinued prior to Day 92 and follow up visits (Days 92 and/or 120) may be cancelled; †Phoenix® WinNonlin® 8.2, Certara, Princeton, NJ. AUC, area under plasma concentration-time curve; BMI, body mass index; CPT, Child-Pugh-Turcotte; CI, confidence interval; $C_{\text{max}}$, maximum concentration; GLSM, geometric least-square mean; LC-MS/MS, liquid chromatography–tandem mass spectrometry.
### Results

#### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Moderate HI n=10</th>
<th>HC n=10</th>
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<tbody>
<tr>
<td>Age, y (range)</td>
<td>56 (39–71)</td>
<td>55 (31–69)</td>
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<tr>
<td>Sex at birth, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (70)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (30)</td>
<td>3 (30)</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>BMI, kg/m² (range)</td>
<td>31.9 (23.5–37.8)</td>
<td>29.5 (25.0–36.1)</td>
</tr>
<tr>
<td>CLcr, mL/min (range)</td>
<td>113.2 (69.4–224.5)</td>
<td>117.1 (90.4–192.9)</td>
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<td>CPT score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7 (70)</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>3 (30)</td>
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</tbody>
</table>

### Safety

- LEN was generally well tolerated
- None experienced serious or Grade 3 or 4 treatment emergent adverse events
- Laboratory abnormalities:
  - 4 volunteers 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
  - No clinically significant changes in vital signs or electrocardiograms

CLcr, creatinine clearance by Cockcroft-Gault formula; SD, standard deviation.
LEN PK in Moderate HI and Matched HC

- LEN AUC_{int} and C_{max} were ~47% and ~161% higher, respectively, in volunteers with moderate HI relative to their matched HC.
- LEN plasma protein binding, median T_{max} and t_{1/2} were similar in both groups.
- 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.

PK parameters presented to 3 significant figures as mean (% coefficient of variation) except maximum time (T_{max}) and half-life (t_{1/2}) which are presented as median (Q1, Q3). AUC_{int}, AUC from time 0 to infinity; AUC_{last}, AUC from time 0 to last measurable concentration; INR, international normalized ratio; SD, standard deviation.
Conclusion

- LEN AUC and $C_{max}$ were 1.5- and 2.6-fold higher, respectively, in volunteers with moderate hepatic impairment compared with 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 people with mild to moderate hepatic impairment.

We extend our thanks to the volunteers for their participation in this study.

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