Pharmacokinetics of Lenacapavir in Participants With Severe Renal Impairment

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Introduction

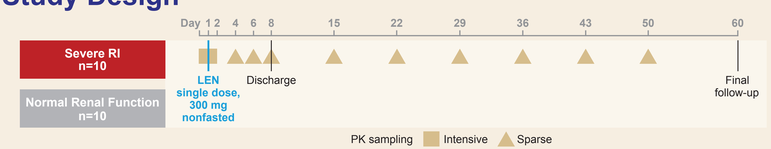
- Lenacapavir (LEN; 300 mg), a novel, first-in-class, selective inhibitor of HIV-1 capsid function, is in clinical development for the treatment and prevention of HIV-1 infection
- Both preclinical and clinical observations suggest fecal excretion as the primary pathway, with renal excretion as a minor pathway of LEN elimination (<1% of dose)
- To support clinical development of LEN in individuals with impaired renal function, assessed based on creatinine clearance using the Cockcroft-Gault method ($CrCl_{CG}$), the pharmacokinetics (PK) and safety of LEN were evaluated in participants with severe renal impairment (RI; $CrCl_{CG}$15–≤29 mL/min; stage 4–5 chronic kidney disease) and matched healthy controls ($CrCl_{CG}$ ≥90 mL/min)

Objectives

- To evaluate the single-dose PK and safety of LEN in individuals with severe RI ($CrCl_{CG}$ 15–≤29 mL/min) compared with matched healthy controls with normal renal function ($CrCl_{CG}$ ≥90 mL/min)

Methods

Study Design



- Multicenter, open-label, parallel-design, single-dose PK study
- Renal function was assessed based on $CrCl_{CG}$
  - $CrCl_{CG}$ 15–≤29 mL/min for severe RI (stage 4–5 chronic kidney disease) and ≥90 mL/min for matched healthy controls with normal renal function
- LEN 300 mg was administered in the nonfasted state to participants with severe RI and normal renal function
- Healthy participants with normal renal function were matched to participants with severe RI based on age (± 10 y), sex at birth, and body mass index (BMI; ±20%)
- Safety was monitored throughout the study by assessment of vital signs, physical examinations, electrocardiograms (ECGs), clinical laboratory tests, and adverse events (AEs)
- Plasma concentrations of LEN were quantified using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method
- Plasma protein binding of LEN was assessed using equilibrium dialysis and LC-MS/MS to determine the percentage of fraction unbound
- A parametric analysis of variance model appropriate for a parallel design was fitted to logarithmically transformed PK parameters (area under curve [AUC] and maximal concentration [C_{max}]); 90% confidence intervals (CIs) were constructed for geometric least-squares mean ratios (GLSMRs) of these parameters between the severe RI and normal renal function groups

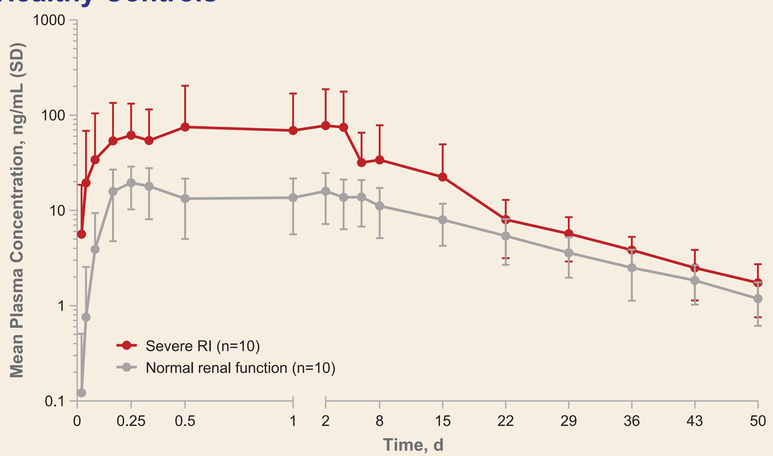
Results

Baseline Characteristics

Participants	Severe RI	Normal Renal Function
Completed, n	10	10
Male/female, n	7/3	7/3
Mean age, y (SD)	63 (17)	60 (15)
Mean BMI, kg/m² (SD)	25.8 (5.2)	26.9 (2.5)
Mean $CrCl_{CG}$, mL/min (SD)	22 (4.1)	103 (13)
Minimum–maximum $CrCl_{CG}$, mL/min	16–31	90–130

SD, standard deviation.

LEN PK in Participants With Severe RI and Matched Healthy Controls



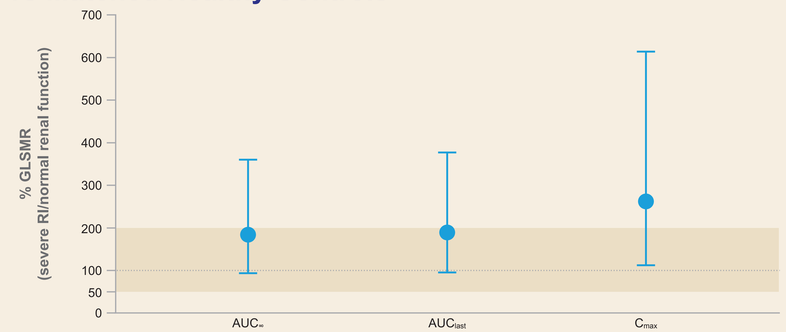
PK Parameter*	Severe RI n=10	Normal Renal Function n=10	%GLSMR (90% CI)
AUC_{∞}, h·ng/mL	19,000 (98)	7400 (48)	184 (93.6, 360)
AUC_{last}, h·ng/mL	18,300 (101)	6840 (49)	189 (95.2, 377)
C_{max}, ng/mL	118 (129)	22.1 (44)	262 (112, 614)
T_{max}, h	8.00 (6.00, 24.0) [0.33 d]	6.00 (6.00, 8.00) [0.25 d]	—
$t_{1/2}$, h	234 (178, 354) [9.75 d]	318 (270, 357) [13.3 d]	—

*AUC from time 0 to ∞ (AUC_{∞}), AUC from time 0 to last measured concentration (AUC_{last}), and C_{max} presented as mean (% coefficient of variation), and time to C_{max} (T_{max}) and half-life ($t_{1/2}$) presented as median (quartiles 1, 3).

Similar Estimated Fraction Unbound to Plasma Proteins

Mean Fraction Unbound, % (SD)	Severe RI n=10	Normal Renal Function n=10
LEN	0.246 (35.3)	0.206 (27.2)

Comparison of PK Changes in Participants With Severe RI vs Matched Healthy Controls*



*Comparable exposures were indicated by GLSMR of 100% represented as *dotted line* and no clinically meaningful PK change interval of 50–200% GLSMR represented by *shaded area*.

Safety

- Most treatment-emergent AEs were Grade 1 or 2 in severity
- A Grade 1 serious AE (melena due to hospitalization) was reported for 1 participant in the severe RI group; the AE resolved and was not considered related to study drug
- No deaths, Grade 4 AEs, or AEs that led to premature study discontinuation were observed
- No clinically significant changes in vital signs or ECGs were observed
- No clinically significant trends in laboratory parameters or evidence of hepatotoxicity were observed in either group

Conclusions

- Single-dose LEN 300 mg was safe and generally well tolerated in this study
- Exposures of LEN were higher in participants with severe RI vs matched healthy controls
  - Increases in exposure were potentially due to the broader effect of uremic toxins on P-glycoprotein (ie, decreased activity of P-glycoprotein-mediated LEN transport) and alterations in metabolic enzymes
- The numerical 84% and 162% increases in LEN exposures (AUC and C_{max}, respectively) in participants with severe RI are unlikely to be clinically relevant and do not warrant dose adjustment based on the overall safety profile and totality of available LEN safety data across clinical studies
  - Prior clinical study data showed that a <2-fold change (50–200% interval) in exposure was not deemed clinically meaningful
- The results of this study support inclusion of patients with mild, moderate, and severe RI in clinical trials including LEN

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