Poster #1940

Pharmacokinetics of Co-Administered HCV Protease Inhibitor Grazoprevir (MK-5172) and NS5A Inhibitor Elbasvir (MK-8742) in Volunteers With End-Stage Renal Disease on Hemodialysis or Severe Renal Impairment Not on Hemodialysis

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Abstract

Background: Grazoprevir (MK-5172) is a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS3/4A protease and elbasvir (MK-8742) is a potent, once-daily inhibitor of the HCV NS5A replication complex that are being developed as a fixed-dose combination therapy for the treatment of chronic HCV infection. This study evaluated the steady-state plasma pharmacokinetics (PK) of grazoprevir and elbasvir when coadministered in volunteers with end-stage renal disease (ESRD) on hemodialysis (HD) or severe renal impairment (SRI) not on hemodialysis.

Methods: This was an open-label, multiple-dose (MD) study to evaluate the PK and safety of grazoprevir and elbasvir when coadministered in subjects with ESRD on HD and non-HD days (Part 1, n=8) and subjects with SRI (Part 2, n=8). The PK in Parts 1 and 2 were compared with those in healthy matched control (HMC) subjects who were matched for mean age, BMI, and gender in Parts 1 and 2 (N=8). All subjects received daily doses of 100 mg grazoprevir and 50 mg elbasvir for 10 days. In Part 1, PK assessments were performed on non-HD Day 9 and HD Day 10 to quantify grazoprevir and elbasvir removal during HD.

Results: Multiple doses of coadministered grazoprevir and elbasvir were generally well tolerated in subjects with SRI, with ESRD on HD, and in HMC. The $AUC_{0\text{-}24}$ of grazoprevir and elbasvir in subjects with ESRD on HD were similar when comparing HD to non-HD days, with geometric mean ratios (GMRs) [90% confidence intervals (CI)] of 0.97 [0.87, 1.09] and 1.14 [1.08, 1.21], respectively. Dialysis removed <0.5% of grazoprevir from plasma and did not remove elbasvir (0%). The PK of grazoprevir and elbasvir were similar between subjects with ESRD and HMC, with $AUC_{0\text{-}24}$ GMRs [90% CIs] for grazoprevir and elbasvir of 0.83 [0.56, 1.22] and 0.99 [0.75, 1.30] (ESRD HD day/HMC) and 0.85 [0.58, 1.25] and 0.86 [0.65, 1.14] (ESRD non-HD day/HMC), respectively. In comparison, the plasma concentrations of grazoprevir and elbasvir were higher in subjects with SRI relative to HMC, with $AUC_{0\text{-}24}$ GMR [90% CI] of 1.65 [1.09, 2.49] and 1.86 [1.38, 2.51], respectively.

Conclusions: Coadministration of grazoprevir and elbasvir was generally well tolerated in subjects with ESRD on HD and in subjects with SRI. HD does not significantly affect grazoprevir and elbasvir PK in ESRD patients, with negligible removal of grazoprevir and elbasvir by HD. The PK of grazoprevir and elbasvir are not significantly altered in subjects with ESRD requiring HD compared to HMC. However, grazoprevir and elbasvir concentrations were higher in subjects with severe renal impairment not on HD compared to matched healthy subjects, consistent with observations that renal impairment can alter the PK of hepatically eliminated drugs.

Background

- Grazoprevir (MK-5172) is a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS3/4A protease and elbasvir (MK-8742) is a potent, once-daily inhibitor of the HCV NS5A replication complex that are being developed as a fixed-dose combination therapy for the treatment of chronic HCV infection
- Preclinical data and Phase 1 studies demonstrate that <1% of both grazoprevir and elbasvir are renally excreted. However, it has been shown that severe renal impairment (SRI) may indirectly affect the liver clearance of compounds that are primarily hepatically eliminated. Since a proportion of patients with chronic HCV also have renal impairment, it is important to evaluate the impact of renal impairment on the plasma PK of grazoprevir and elbasvir

Aims

- To understand the effect of severe renal impairment on the plasma PK of grazoprevir and elbasvir in order to guide dosing recommendations for patients with severe renal impairment with or without dialysis
- To examine the degree to which grazoprevir and elbasvir are removed from plasma by hemodialysis (HD)
- To assess the safety and tolerability of grazoprevir and elbasvir when coadministered in subjects with renal impairment

Subjects and Methods

- **Study design:** Open-label, two-part, multiple-dose (MD) study
- **Subjects:** A total of 24 non-tobacco-using male and female subjects between the ages of 18 and 80 years (inclusive), with a body mass index (BMI) ≥18 to ≤40 kg/m² (inclusive) were enrolled:
  - **Part 1:** 8 subjects with ESRD on a stable regimen of HD within three months prior to the first dose enrolled
  - **Part 2:** 8 subjects with SRI with estimated glomerular filtration rate [eGFR] <30 mL/min and not on HD
  - **After completion of Parts 1 and 2:** 8 healthy matched control (HMC) subjects with eGFR >80 mL/min, matched to the mean of subjects with impaired renal function in Parts 1 and 2 (for age [± 10 years], BMI [± 10%], and gender [similar proportion of males and females as in Parts 1 and 2])
- **Treatments:** All subjects received once-daily (QD) oral doses of 100 mg grazoprevir and 50 mg elbasvir for 10 days. In Part 1 on HD days, HD was timed to occur after the median T_{max} of grazoprevir and elbasvir (5 hours postdose)
- **Assessments:**
  - Safety: Adverse experiences (AEs), physical examination, vital signs, electrocardiograms (ECGs), laboratory safety tests
  - Grazoprevir and elbasvir PK:
    - **Plasma PK** samples for determination of PK parameters were collected from each subject at predose and at specified time points over 120 hours following last dose on Day 10. In Part 1 of the study, since Day 10 was the HD day for subjects with ESRD, blood samples were also collected from these subjects at predose and at selected time points over 24 hours on Day 9 (non-HD day)
      - Trough samples for steady-state assessment were collected on Days 5 through 10 for ESRD subjects and Days 6 through 10 for SRI and HMC subjects
    - **Dialysate PK** samples were collected from each ESRD subject for 1 minute every half hour during HD (on Day 10), starting at 5 hours through 9 hours
    - **Urine PK** samples were collected (if available) through 24 hours postdose on Day 9 (for ESRD subjects only) and through 72 hours postdose on Day 10 for all subjects
    - **Protein binding** was determined from plasma samples collected at 3 and 8 hours postdose on Day 10
  - Statistical analyses: Exposure parameters were natural-log transformed and analyzed with a linear mixed-effects model, with data from both parts pooled. The model contained a fixed effect for population (ESRD on non-HD day, ESRD on HD day, SRI, HMC), a random effect for subject, and gender, age, and BMI as covariates. The least-squares means (LSMs) and corresponding 95% confidence intervals (CIs) were calculated by population, and the differences in population LSMs and corresponding 90% CIs were estimated for each parameter. The back-transformed summary results were reported for each exposure parameter as the geometric means (GMs) and corresponding 95% CIs as well as the geometric mean ratios (GMRs) for each comparison and corresponding 90% CIs

Results and Discussion

Subject demographics

- Of the 24 subjects enrolled, 14 were White and 10 were Black/African American. All 24 subjects completed the study (**Table 1**)

Table 1. Subject characteristics

	Part 1 ESRD on HD	Part 2 Severe Renal Insufficiency	Healthy Matched Controls
Entered:	8	8	8
Completed:	8	8	8
Male N (age range, years)	5 (40 - 61)	4 (54 - 68)	4 (47 - 63)
Female N (age range, years)	3 (38 - 61)	4 (59 - 75)	4 (52 - 58)
Height (mean and range, cm):	172.9 (158 - 184)	164.6 (146 - 179)	166.9 (151 - 189)
Weight (mean and range, kg):	92.38 (73.4 - 121.2)	78.75 (57.3 - 97.0)	82.05 (68.3 - 107.5)
BMI (mean and range, kg/m²)	30.79 (26.90 - 35.80)	28.63 (24.20 - 34.10)	29.35 (26.80 - 31.60)
Race:			
White	1	5	8
Black/African American	7	3	0
eGFR (mean and range, mL/min/1.73 m²)	†	18.0 (11.5 - 23.5)	93.4 (80.0 - 124.0)

†eGFR for ESRD subjects was not obtained due to anuria.

Safety and tolerability

- Administrations of QD oral doses of 100 mg grazoprevir and 50 mg elbasvir for 10 days were generally well tolerated in subjects with ESRD on HD, in subjects with SRI, and in the HMC subjects
- There were no deaths, serious AEs, or discontinuations due to AEs reported during the study. There were also no consistent, treatment-related changes for any of the population groups in the safety laboratory profiles, vital signs, or ECG assessments during the study
- Ten subjects reported a total of 17 AEs (13 mild, 4 moderate), 8 of which were considered drug-related by the investigator: 3 in 2 ESRD subjects on HD (1 with oral paraesthesia and myalgia and 1 with muscular weakness), 3 in 2 SRI subjects (1 with headache and muscular weakness and 1 with headache), and dry mouth and headache reported by 1 HMC subject

Pharmacokinetics of grazoprevir and elbasvir

- Multiple doses of grazoprevir and elbasvir coadministered to subjects with ESRD receiving hemodialysis resulted in similar grazoprevir and elbasvir exposures when comparing HD to non-HD days and when comparing to grazoprevir and elbasvir PK parameters in HMC subjects **(Figures 1** and **2, Tables 2** and **3)**
  - GMRs for $AUC_{0\text{-}24}$ and C_{24} were all close to unity (± 20%), with CIs that all contained 1.0, indicating no statistically significant differences
  - Dialysis did not remove any elbasvir (0%) and removed <0.5% of grazoprevir from plasma. During the 4-hour HD session, the geometric mean amount of grazoprevir recovered from the dialysate was 0.0172 mg, with dialysis clearance (based on plasma) of 1.45 mL/min
  - Renal clearance could not be determined in subjects with ESRD due to anuria
- Based on GMRs for $AUC_{0\text{-}24}$, C_{max}, and C_{24}, the exposures of grazoprevir and elbasvir were 60% - 66% and 66% – 107% higher, respectively, in subjects with SRI relative to those in HMC subjects (**Figures 1** and **2, Tables 4** and **5**)
  - CL/F and Vz/F were both ~39% lower for grazoprevir and 46% and 37% lower, respectively, for elbasvir in subjects with SRI relative to that in HMC subjects, while the apparent terminal elimination $t_{½}$ was similar between these two groups for both analytes
  - Renal clearance was negligible for both grazoprevir (<0.06 L/hr) and elbasvir (<0.02 L/hr) in subjects with SRI and HMC subjects, with ≤0.15% dose excreted renally for either analyte
- The unbound fraction (fu) (arithmetic mean ± standard deviation) for grazoprevir was similar in subjects with SRI (0.022 ± 0.004) relative to HMC subjects (0.017 ± 0.003) or subjects with ESRD (0.018 ± 0.005). The elbasvir fu was <0.005 in all three populations of subjects; consequently, minor differences in elbasvir fu among the populations could not be detected
- Steady state was achieved on or before Hour 24 of Day 7 for both grazoprevir and elbasvir in all three populations of subjects (ESRD, SRI, and HMC)

Figure 1. Arithmetic mean plasma concentration-time profiles of grazoprevir (MK-5172) following multiple oral doses of 100 mg grazoprevir and 50 mg elbasvir administered to subjects with renal impairment and to healthy matched control subjects (n = 8 for subjects with ESRD on non-hd day 9, n = 8 for subjects with ESRD on HD day 10, n = 8 for subjects with severe renal insufficiency, and n = 8 for healthy matched control subjects) (inset = semi-log scale; LOQ = 1.30 nM)

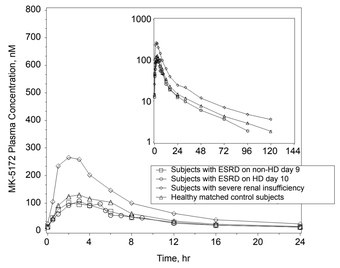

Figure 2. Arithmetic Mean plasma concentration-time profiles of elbasvir (MK-8742) following multiple oral doses of 100 mg grazoprevir and 50 mg elbasvir administered to subjects with renal impairment and to healthy matched control subjects (n = 8 for subjects with ESRD on non-HD day 9, n = 8 for subjects with ESRD on HD day 10, n = 8 for subjects with severe renal insufficiency, and n = 8 for Healthy matched control subjects) (inset = semi-log scale; LOQ = 0.283 nM)

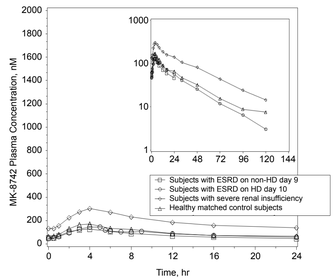

Table 2. Statistical comparison of plasma pharmacokinetics of grazoprevir following multiple oral dose co-administration of 100 mg grazoprevir and 50 mg elbasvir for 10 days to subjects with ESRD on hemodialysis (HD) day 10 and non-hemodialysis (non-HD) day 9 and to healthy matched control subjects (n = 8 for each comparison population)

Grazoprevir Pharmacokinetic Parameter	ESRD on HD Day 10		ESRD on Non-HD Day 9		Healthy Matched Control			
	GM	95% CI	GM	95% CI	GM	95% CI	rMSE†	Total SD†
$AUC_{0\text{-}24}$‡ (µM•hr)	0.944	(0.671, 1.33)	0.969	(0.689, 1.36)	1.14	(0.843, 1.54)	0.119	0.405
C_{max}‡ (µM)	0.135	(0.0882, 0.206)	0.141	(0.0920, 0.215)	0.154	(0.106, 0.224)	0.253	0.505
C24‡ (nM)	11.3	(8.03, 15.8)	11.4	(8.16, 16.1)	14.5	(10.7, 19.6)	0.204	0.405
CL/F‡, ¶ (L/hr)	138	(98.1, 194)	135	(95.6, 189)	114	(84.5, 155)	0.119	0.405
Vz/F‡ (L)	5430	(3660, 8050)			5760	(4180, 7930)	0.428	
T_{max}§ (hr)	2.50	(0.50, 7.00)	2.00	(1.00, 6.00)	2.50	(1.00, 6.00)		
Apparent terminal $t_{½}$‖ (hr)	28.38	20.88			35.18	19.64		

Grazoprevir Pharmacokinetic Parameter	ESRD on HD Day 10/ESRD on Non-HD Day 9		ESRD on HD Day 10/Healthy Matched Control		ESRD on Non-HD Day 9/Healthy Matched Control	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
$AUC_{0\text{-}24}$‡ (µM•hr)	0.97	(0.87, 1.09)	0.83	(0.56, 1.22)	0.85	(0.58, 1.25)
C_{max}‡ (µM)	0.96	(0.75, 1.22)	0.88	(0.54, 1.42)	0.92	(0.57, 1.48)
C_{24}‡ (nM)	0.98	(0.81, 1.19)	0.78	(0.53, 1.14)	0.79	(0.54, 1.16)
CL/F‡, ¶ (L/hr)	1.03	(0.92, 1.15)	1.21	(0.82, 1.78)	1.18	(0.80, 1.73)
Vz/F‡ (L)			0.94	(0.63, 1.42)		

Single daily oral dose of 100 mg grazoprevir (1 x 100 mg tablet) and 50 mg elbasvir (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.
†rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model rMSE×100% approximates the within-subject %CV (except for Vz/F, for which rMSE approximates the total %CV) on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model.
‡Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values.
§Median (min, max) reported for T_{max}.
‖The geometric mean and geometric CV reported for apparent terminal $t_{½}$.
¶CL/F values are based on $AUC_{0\text{-}24}$.
GM=Geometric least-square mean; GMR=Geometric least-square mean ratio; CI=Confidence interval.
Since Vz/F is not available for ESRD subjects on Day 9, only the rMSE is presented from the ANCOVA fixed effects model.

Table 3. Statistical comparison of plasma pharmacokinetics of elbasvir Following multiple oral dose co-administration of 100 mg grazoprevir and 50 mg elbasvir for 10 Days to subjects with ESRD on hemodialysis (HD) day 10 and non-hemodialysis (non-HD) day 9 and to Healthy matched control subjects (N = 8†† for each comparison population)

Elbasvir Pharmacokinetic Parameter	ESRD on HD Day 10		ESRD on Non-HD Day 9		Healthy Matched Control			
	GM	95% CI	GM	95% CI	GM	95% CI	rMSE†	Total SD†
$AUC_{0\text{-}24}$‡ (µM•hr)	2.16	(1.69, 2.77)	1.89	(1.48, 2.42)	2.19	(1.76, 2.72)	0.057	0.291
C_{max}‡ (µM)	0.154	(0.118, 0.200)	0.137	(0.105, 0.178)	0.163	(0.129, 0.206)	0.120	0.311
C_{24}‡ (nM)	58.2	(43.7, 77.5)	46.9	(35.2, 62.4)	60.9	(47.3, 78.5)	0.064	0.338
CL/F‡ (L/hr)	26.2	(20.5, 33.5)	29.9	(23.4, 38.3)	25.9	(20.8, 32.2)	0.057	0.291
Vz/F‡ (L)	857	(641, 1150)			901	(699, 1160)	0.315	
T_{max}§ (hr)	5.00	(3.00, 5.00)	4.00	(3.00, 4.00)	4.00	(2.00, 4.00)		
Apparent terminal $t_{½}$‖ (hr)	23.04	6.34			25.02	19.08		

Elbasvir Pharmacokinetic Parameter	ESRD on HD Day 10/ESRD on Non-HD Day 9		ESRD on HD Day 10/Healthy Matched Control		ESRD on Non-HD Day 9/Healthy Matched Control	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
$AUC_{0\text{-}24}$‡ (µM•hr)	1.14	(1.08, 1.21)	0.86	(0.65, 1.14)	0.99	(0.75, 1.30)
C_{max}‡ (µM)	1.12	(1.00, 1.26)	0.84	(0.62, 1.13)	0.94	(0.70, 1.27)
C_{24}‡ (nM)	1.24	(1.17, 1.32)	0.77	(0.56, 1.06)	0.95	(0.69, 1.32)
CL/F‡, ¶ (L/hr)	0.88	(0.83, 0.92)	1.16	(0.88, 1.53)	1.01	(0.77, 1.34)
Vz/F‡ (L)					0.95	(0.70, 1.30)

Single daily oral dose of 100 mg grazoprevir (1 x 100 mg tablet) and 50 mg elbasvir (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.
†rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE×100% approximates the within-subject %CV (except for Vz/F, for which rMSE approximates the total %CV) on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model.
‡Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values.
§Median (min, max) reported for T_{max}.
‖The geometric mean and geometric CV reported for apparent terminal $t_{½}$.
¶CL/F values are based on $AUC_{0\text{-}24}$.
††For HMC, N = 7 for parameters apparent terminal $t_{½}$ and Vz/F, since values were not calculated for Subject AN 0018 due to ill-defined terminal phase.
GM=Geometric least-square mean; GMR=Geometric least-square mean ratio; CI=Confidence interval.
Since Vz/F is not available for ESRD subjects on Day 9, only the rMSE is presented from the ANCOVA fixed effects model.

Table 4. Statistical Comparison of plasma and urine pharmacokinetics of grazoprevir following multiple oral doses of 100 mg grazoprevir and 50 mg elbasvir administered for 10 days to subjects with severe renal insufficiency and to healthy control subjects (n = 8 for each comparison population)

Grazoprevir Pharmacokinetic Parameter	Severe Renal Insufficiency		Healthy Matched Control		Severe Renal Insufficiency/ Healthy Matched Control			
	GM	95% CI	GM	95% CI	GMR	90% CI	rMSE†	Total SD†
$AUC_{0\text{-}24}$‡ (µM•hr)	1.88	(1.23, 2.86)	1.14	(0.843, 1.54)	1.65	(1.09, 2.49)	0.119	0.405
C_{max}‡ (µM)	0.255	(0.152, 0.429)	0.154	(0.106, 0.224)	1.66	(0.99, 2.77)	0.253	0.505
C_{24}‡ (nM)	23.3	(15.4, 35.2)	14.5	(10.7, 19.6)	1.60	(1.06, 2.42)	0.204	0.405
CL/F‡, ¶ (L/hr)	69.4	(45.6, 106)	114	(84.5, 155)	0.61	(0.40, 0.92)	0.119	0.405
Vz/F‡ (L)	3490	(2320, 5260)	5760	(4180, 7930)	0.61	(0.39, 0.94)	0.428	
T_{max}§ (hr)	3.00	(0.50, 6.00)	2.50	(1.00, 6.00)				
Apparent terminal $t_{½}$‖ (hr)	36.30	30.53	35.18	19.64				
feu72hr††	0.000211	(0.0000906, 0.000493)	0.000631	(0.000500, 0.000797)				
CL_R†† (L/hr)	0.00961	(0.00473, 0.0195)	0.0561	(0.0386, 0.0813)				

Single daily oral dose of 100 mg grazoprevir (1 x 100 mg tablet) and 50 mg elbasvir (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days1 to 10.
†rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model rMSE×100% approximates the within-subject %CV (except for Vz/F, for which rMSE approximates the total %CV) on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model. ‡Back-transformed least-squares geometric means, ratios, and CI for linear mixed-effect model performed on natural log-transformed values. §Median (min, max) reported for T_{max}. ‖The geometric mean and geometric CV reported for apparent terminal $t_{½}$. ¶CL/F values are based on $AUC_{0\text{-}24}$. †† For HMC, N=7 for parameters apparent terminal $t_{½}$ and Vz/F, since values were not calculated for Subject AN 0018 due to ill-defined terminal phase. ††feu=fraction of dose excreted in urine over the collection interval; CL_R=renal clearance (based on amount excreted over 24 hr/$AUC_{0\text{-}24}$). Non-model-based GM and 95% CI reported for feu and CL_R referencing a t-distribution. GM=Geometric mean; GMR=Geometric least-square mean ratio; CI=Confidence interval. Since Vz/F is not available for ESRD subjects on Day 9, only the rMSE is presented from the ANCOVA fixed effects model.

Table 5. Statistical Comparison of plasma and urine pharmacokinetics of elbasvir following multiple oral doses of 100 mg grazoprevir and 50 mg elbasvir administered for 10 days to subjects with severe renal insufficiency and to healthy control subjects (n = 8†† for each comparison population)

Elbasvir Pharmacokinetic Parameter	Severe Renal Insufficiency		Healthy Matched Control		Severe Renal Insufficiency/ Healthy Matched Control			
	GM	95% CI	GM	95% CI	GMR	90% CI	rMSE†	Total SD†
$AUC_{0\text{-}24}$‡ (µM•hr)	4.07	(3.01, 5.52)	2.19	(1.76, 2.72)	1.86	(1.38, 2.51)	0.057	0.291
C_{max}‡ (µM)	0.271	(0.196, 0.373)	0.163	(0.129, 0.206)	1.66	(1.21, 2.28)	0.120	0.311
C_{24}‡ (nM)	126	(88.6, 179)	60.9	(47.3, 78.5)	2.07	(1.46, 2.93)	0.064	0.338
CL/F‡, ¶ (L/hr)	13.9	(10.3, 18.9)	25.9	(20.8, 32.2)	0.54	(0.40, 0.72)	0.057	0.291
Vz/F‡,†† (L)	569	(420, 772)	901	(699, 1160)	0.63	(0.45, 0.89)	0.315	
T_{max}§ (hr)	4.00	(4.00, 6.00)	4.00	(2.00, 4.00)				
Apparent terminal $t_{½}$‖, †† (hr)	28.97	18.26	25.02	19.08				
feu72hr‡‡	0.00150	(0.00108, 0.00208)	0.000979	(0.000574, 0.00167)				
CL_R‡‡ (L/hr)	0.0114	(0.00883, 0.0147)	0.0180	(0.0125, 0.0260)				

Single daily oral dose of 100 mg grazoprevir (1 x 100 mg tablet) and 50 mg elbasvir (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.
†rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE×100% approximates the within-subject %CV (except for Vz/F, for which rMSE approximates the total %CV) on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model. ‡Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values. §Median (min, max) reported for T_{max}. ‖The geometric mean and geometric CV reported for apparent terminal $t_{½}$. ¶CL/F values are based on $AUC_{0\text{-}24}$. †† For HMC, N=7 for parameters apparent terminal $t_{½}$ and Vz/F, since values were not calculated for Subject AN 0018 due to ill-defined terminal phase. ‡‡feu=fraction of dose excreted in urine over the collection interval; CL_R=renal clearance (based on amount excreted over 24 hr/$AUC_{0\text{-}24}$). Non-model-based GM and 95% CI reported for feu and CL_R referencing a t-distribution. GM=Geometric mean; GMR=Geometric least-square mean ratio; CI=Confidence interval. Since Vz/F is not available for ESRD subjects on Day 9, only the rMSE is presented from the ANCOVA fixed effects model.

Conclusions/Discussion

- Coadministration of grazoprevir and elbasvir was generally well tolerated in subjects with ESRD on HD and in subjects with SRI
- HD does not significantly affect grazoprevir and elbasvir PK in ESRD patients. The removal of grazoprevir and elbasvir by HD is negligible. The very high plasma protein binding for both analytes, and in particular for elbasvir, is consistent with the small amounts of grazoprevir and no elbasvir quantified in dialysate, as plasma protein-bound drug complexes are too large to be removed by HD
- Grazoprevir and elbasvir concentrations were higher in subjects with severe renal impairment not on HD compared to matched healthy subjects. The increases in exposure to grazoprevir and elbasvir and decreases in apparent CL/F and Vz/F in the presence of SRI are consistent with prior observations that renal impairment may affect the disposition of compounds that are hepatically eliminated. This effect is potentially due to the influence of high levels of uremic toxins, parathyroid hormone (PTH), and cytokines that can inhibit hepatic CYPs and transporters[1,2]
- Changes in protein binding are not likely to account for the observed PK differences for grazoprevir and elbasvir
- A Phase 2/3 trial of grazoprevir and elbasvir in HCV-infected patients with renal insufficiency with or without hemodialysis (C-SURFER) is ongoing

Current Phase 3 Program for Grazoprevir + Elbasvir

Study	Geno-type	Fibrosis Staging	Treatment History	Co-Morbidity	Regimen (Weeks)
C-EDGE TN	1, 4, 6	± Cirrhosis	TN	–	12, no RBV
C-EDGE CO-INFECTION	1, 4, 6	± Cirrhosis	TN	HIV	12, no RBV
C-EDGE CO-STAR	1, 4, 6	± Cirrhosis	TN	OST; ± HIV	12, no RBV
C-EDGE TE	1, 4, 6	± Cirrhosis	PR-TE	± HIV	12 or 16, ±RBV
C-SURFER	1	Non-cirrhotic	TN	CKD 4-5	12, no RBV
C-EDGE IBLD	1, 4, 6	± Cirrhosis	TN/PR-TE	IBLD ± HIV	12, no RBV

TN=Treatment-naïve; OST=Opiate Substitution Therapy; PR-TE= Peginterferon/ribavirin treatment-experienced; CKD=Chronic Kidney Disease; IBLD=Inherited Blood Disorders

References

1. Zhang Y, Zhang L, Abraham S, et al. *Clin Pharmacol Therapeutics.* 2009;85(3):305-311.
2. Dreisbach AW, Lertora J. *Clin Pharmacol Therapeutics.* 2009;86(5):1065-1074.

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