No Evidence of Pharmacokinetic Drug-Drug Interaction in Healthy Subjects Between Coadministered Grazoprevir (MK-5172)/Elbasvir (MK-8742) and Sofosbuvir

William L. Marshall*[1]; Wendy W. Yeh[1]; Crystal Bethel-Brown[2]; Daria Stypinski[2]; Patrice Auger[2]; Christine Brandquist[2]; Dana Gill[2]; John Brejda[2]; Luzelena Caro[1]; Patricia Jumes[1]; Xiaobi Huang[1]; Zifang Guo[1]; Monika Martinho[1]; H-P Feng[1]; Danielle Armas[2]; Marian Iwamoto[1]; Joan R. Butterton[1]

[1]Merck & Co., Inc., Kenilworth, NJ, USA; [2]Celerion, Tempe, AZ, USA

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Abstract

Background and aims: Grazoprevir (MK-5172), a potent inhibitor of the hepatitis C virus (HCV) NS3/4A protease, and elbasvir (MK-8742), a potent inhibitor of the HCV NS5A replication complex, are being developed as a once-daily (QD) fixed-dose combination therapy for the treatment of chronic HCV infection. This study evaluated the effect of grazoprevir and elbasvir on the pharmacokinetics of sofosbuvir (SOF), an HCV NS5B inhibitor, when coadministered in healthy subjects.

Methods: This was an open-label, 2-period, fixed-sequence study to assess the effect of multiple oral doses of grazoprevir and elbasvir on the pharmacokinetics of a single oral dose of SOF. Sixteen (16) healthy adult male and female subjects were enrolled. In Period 1, subjects received a single oral 400-mg dose of SOF. Following an 8-day washout period, multiple oral doses of 200 mg grazoprevir and 50 mg elbasvir were coadministered QD from Days 1 to 15, inclusive, in Period 2. On Day 11, a single oral dose of SOF was coadministered with the dose of grazoprevir and elbasvir. Plasma pharmacokinetic parameters of SOF and its principal nucleoside metabolite (GS-331007) were measured in Period 1 and following the dose on Day 11 in Period 2.

Results: SOF + grazoprevir + elbasvir/SOF alone geometric mean ratios (GMRs) [90% confidence intervals (90% CIs)] for plasma SOF $AUC_{0-\infty}$ and C_{max} were 2.43 [2.12, 2.79] and 2.27 [1.72, 2.99], respectively. These changes in SOF exposure are not considered to be clinically meaningful based on the safety margins of SOF. The GMRs [90% CIs] for plasma GS-331007 $AUC_{0-\infty}$ and C_{max} for the same comparison were 1.13 [1.05, 1.21] and 0.87 [0.78, 0.96], respectively. These changes in GS-331007 exposure are not considered to be clinically meaningful. Coadministration of SOF, grazoprevir, and elbasvir was generally well tolerated.

Conclusions: Multiple-dose administration of 200 mg grazoprevir and 50 mg elbasvir daily with a single dose of SOF was generally well tolerated by healthy subjects in this study. Coadministration of elbasvir and grazoprevir with SOF had no clinically meaningful effect on the pharmacokinetics of SOF and its metabolite GS-331007. Taken together with the lack of potential for SOF to perpetrate a drug-drug interaction on grazoprevir or elbasvir, these results suggest that SOF, grazoprevir, and elbasvir may be coadministered without dose adjustment.

Background

- Grazoprevir (GZR, MK-5172), a potent inhibitor of the hepatitis C virus (HCV) NS3/4A protease, and elbasvir (EBR, MK-8742), a potent inhibitor of the HCV NS5A replication complex, are principal components of an oral, direct-acting, antiviral regimen for the treatment of HCV infection
- Grazoprevir is a weak CYP3A4 inhibitor, a BCRP inhibitor, and a substrate of CYP3A/P-gp and OATP1B1/1B3 that is administered at 200 mg in healthy subjects to achieve similar exposures to those observed after administration of 100 mg to HCV-infected patients
- Elbasvir is a substrate of CYP3A/P-gp and an inhibitor of BCRP; however, based on in vitro data, it is not a time-dependent inhibitor of CYP3A
- SOF is an HCV-specific NS5B nucleotide inhibitor prodrug indicated for the treatment of chronic HCV genotypes 1, 2, 3, or 4. SOF is a substrate of P-gp and BCRP, while its predominant circulating metabolite, GS-331007, is not.
- A combination of grazoprevir, elbasvir, and sofosbuvir – given their distinct mechanisms of inhibition of HCV replication – may be advantageous in specific settings where increased response rate, shorter duration of therapy, or ribavirin-free regimens would be desirable
- Based on the known metabolic and transporter properties of grazoprevir, elbasvir, and SOF, SOF was not expected to perpetrate a DDI on grazoprevir or elbasvir. However, there was a potential that SOF, a BCRP substrate, may be a victim of BCRP inhibition
- Based on the potential effect that GZR/EBR might have on SOF, and the expected lack of effect of SOF on GZR/EBR pharmacokinetics (PK), the study was designed to assess SOF PK when coadministered with GZR/EBR

Aims

- To assess the effect of multiple doses of grazoprevir and elbasvir on the pharmacokinetic profile of SOF and GS-331007
- To evaluate the safety and tolerability of a single dose of SOF alone, of multiple doses of grazoprevir/elbasvir alone, and of grazoprevir/elbasvir coadministered with SOF

Subjects and Methods

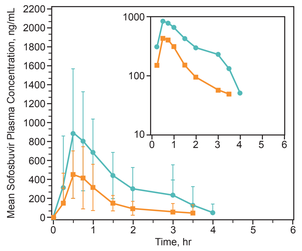
- **Study design:** This was an open-label, 2-period, fixed-sequence study
- **Subjects:** A total of 16 healthy male and female adult subjects between the ages of 18 and 55 years (inclusive), with a body mass index (BMI) ≥19.0 to ≤32.0 kg/m^2, were enrolled
- **Treatments:**
  - Treatment A (Period 1): A single oral dose of 400 mg SOF administered on Day 1
  - Washout period: 8 days
  - Treatment B (Period 2): Multiple QD oral doses of 200 mg grazoprevir and 50 mg elbasvir on Days 1 to 15, with a single oral dose of 400 mg SOF coadministered on Day 11
- **Assessments:**
  - SOF pharmacokinetics: Plasma samples for determination of SOF concentrations were collected from each subject at predose and at specified time points over 120 hours following a single 400-mg SOF dose administered alone on Day 1 of Period 1 and coadministered on Day 11 of Period 2, with QD doses of 200 mg grazoprevir and 50 mg elbasvir administered on Days 1 to 15
  - Safety: Safety was monitored throughout the study via adverse events (AEs), physical examination, vital signs, electrocardiograms (ECGs), and laboratory safety tests
  - Statistical analyses: Exposure parameter values were natural-log transformed and analyzed with a linear mixed-effects model, with a fixed-effect term for treatment (SOF alone, grazoprevir + elbasvir, and SOF + grazoprevir + elbasvir). An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within the same subject. The least-squares means (LSMs) and corresponding 95% confidence intervals (CIs) were calculated by treatment and the differences in treatment 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

Pharmacokinetics of SOF

- Coadministration of SOF with multiple doses of grazoprevir and elbasvir increased the exposure, as measured by AUC and C_{max} values, of SOF compared to single-dose administration of SOF alone (**Figure 1, Table 1**)
  - The GMRs for SOF $AUC_{0-\infty}$, $AUC_{0\text{-last}}$, and C_{max} for SOF + grazoprevir + elbasvir/SOF were approximately 2.4, 2.6, and 2.3, respectively. As described in the sofosbuvir label, coadministration of cyclosporine (a P-gp and BCRP inhibitor) with sofosbuvir is allowed, although it resulted in increased sofosbuvir exposures, with C_{max} GMR (90% CI) of 2.54 (1.87, 3.25) and AUC GMR (90% CI) of 4.53 (3.26, 6.30)
  - The observed median T_{max} value for SOF was unchanged with coadministration of grazoprevir + elbasvir
  - The GM apparent terminal $t_{½}$ values were similar following SOF alone or when coadministered with grazoprevir + elbasvir
- The coadministration of single-dose SOF with multiple doses of grazoprevir + elbasvir resulted in a marginal increase in overall exposure and a marginal decrease in maximum exposure of GS-331007, compared to a single-dose administration of SOF alone (**Figure 2, Table 2**)
  - The GMs for GS-331007 $AUC_{0-\infty}$ and $AUC_{0\text{-last}}$ were slightly increased (~13%) following SOF + grazoprevir + elbasvir compared to SOF alone, while the GM for GS-331007 C_{max} was slightly decreased (~13%) following SOF + grazoprevir + elbasvir compared to SOF alone
  - The GM for GS331007 C_{24} was increased 50% following SOF + grazoprevir + elbasvir compared to SOF alone
  - The observed median GS-331007 T_{max} for SOF was unchanged with coadministration of grazoprevir + elbasvir
  - The observed GS-331007 GM apparent terminal $t_{½}$ value was longer following SOF + grazoprevir + elbasvir compared to SOF alone

Figure 1. Arithmetic mean (SD) plasma concentration-time profiles of sofosbuvir (SOF) following the administration of a single dose of 400 mg sofosbuvir with or without the coadministration of multiple doses of 200 mg MK-5172 (grazoprevir) + 50 mg MK-8742 (elbasvir) QD in healthy adult subjects (N = 16) (Inset = Semi-Log Scale)



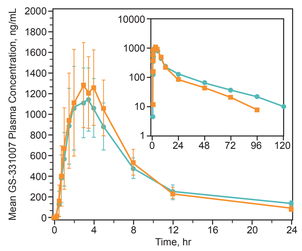
Mean concentrations beyond the 3.5-hour time point for sofosbuvir alone and beyond the 4-hour time point for sofosbuvir + MK-5172 (grazoprevir) + MK-8742 (elbasvir) are not presented since ≥50% of subjects had concentration values below the LLOQ.

Table 1. Statistical comparisons of plasma pharmacokinetics of sofosbuvir (SOF) following the administration of a single dose of 400 mg sofosbuvir with or without the coadministration of multiple doses of 200 mg grazoprevir + 50 mg elbasvir QD in healthy adult subjects

Pharmacokinetic Parameter	Sofosbuvir Alone			Sofosbuvir + Grazoprevir + Elbasvir			Sofosbuvir + Grazoprevir + Elbasvir/Sofosbuvir Alone		
	N¶	GM	95% CI	N††	GM	95% CI	GMR	90% CI	Pseudo Within-Subject %CV†
$AUC_{0-\infty}$‡ (ng•hr/mL)	12	583	(465, 733)	14	1420	(1270, 1580)	2.43	(2.12, 2.79)	18.822
$AUC_{0\text{-last}}$‡ (ng•hr/mL)	16	539	(436, 666)	16	1400	(1260, 1560)	2.59	(2.28, 2.94)	20.461
C_{max}‡ (ng/mL)	16	490	(338, 711)	16	1110	(903, 1370)	2.27	(1.72, 2.99)	44.493
T_{max}§ (hr)	16	0.75	(0.25, 3.50)	16	0.75	(0.25, 3.00)			
Apparent terminal $t_{½}$‖ (hr)	12	0.43	39.88	14	0.39	14.60			

Sofosbuvir Alone: 400 mg (1 x 400 mg tablet) sofosbuvir on Day 1, Period 1.
Sofosbuvir + Grazoprevir + Elbasvir: Coadministration of 400 mg sofosbuvir on Day 11, Period 2, with 200 mg [2 x 100 mg tablets] grazoprevir + 50 mg [1 x 50 mg tablet] elbasvir QD on Days 1 to 15, Period 2.
†Pseudo within-subject %CV = 100*Sqrt[(σ^2_A + σ^2_B - 2*σ_{AB})/2], where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
‡Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
§Median (Minimum, Maximum) reported for T_{max}.
‖Geometric mean and geometric coefficient of variation reported for apparent terminal $t_{½}$.
¶The apparent terminal phase was not well characterized for 4 subjects in Period 1. Consequently, $AUC_{0-\infty}$ and apparent terminal $t_{½}$ were only calculated for 12 out of 16 subjects for sofosbuvir alone.
††The apparent terminal phase was not well characterized for 2 subjects in Period 2. Consequently, $AUC_{0-\infty}$ and apparent terminal $t_{½}$ were only calculated for 14 out of 16 subjects for sofosbuvir + grazoprevir + elbasvir.
Note: C_{24} values were not reported due to all values being below the limit of quantification (BLQ) for all subjects in both treatments.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Figure 2. Arithmetic mean (SD) plasma concentration-time profiles of GS-331007 following the administration of a single dose of 400 mg sofosbuvir with or without the coadministration of multiple doses of 200 mg MK-5172 (grazoprevir) + 50 mg MK-8742 (elbasvir) QD in healthy adult subjects (N = 16) (Inset = Semi-Log Scale)



The mean concentration at the 120-hour time point for sofosbuvir alone is not presented since ≥50% of subjects had concentration values below the LLOQ.

Table 2. Statistical comparisons of plasma pharmacokinetics of GS-331007 following the administration of a single dose of 400 mg sofosbuvir with or without the coadministration of multiple doses of 200 mg grazoprevir + 50 mg elbasvir QD in healthy adult subjects

GS-331007 Pharmacokinetic Parameter	Sofosbuvir Alone			Sofosbuvir + Grazoprevir + Elbasvir			Sofosbuvir + Grazoprevir + Elbasvir/Sofosbuvir Alone		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within-Subject %CV†
$AUC_{0-\infty}$‡ (ng•hr/mL)	16	13,300	(12,300, 14,500)	16	15,000	(13,700, 16,500)	1.13	(1.05, 1.21)	11.434
$AUC_{0\text{-last}}$‡ (ng•hr/mL)	16	12,700	(11,600, 13,900)	16	14,300	(13,100, 15,700)	1.13	(1.04, 1.22)	12.897
C_{max}‡ (ng/mL)	16	1440	(1270, 1630)	16	1250	(1100, 1410)	0.87	(0.78, 0.96)	16.209
C_{24}‡ (ng/mL)	16	86.9	(74.7, 101)	16	133	(117, 150)	1.53	(1.43, 1.63)	10.176
T_{max}§ (hr)	16	3.01	(1.51, 5.01)	16	3.00	(1.99, 5.00)			
Apparent terminal $t_{½}$‖ (hr)	16	23.97	32.29	16	30.66	18.46			

Sofosbuvir Alone: 400 mg (1 x 400 mg tablet) sofosbuvir on Day 1, Period 1.
Sofosbuvir + Grazoprevir + Elbasvir: Coadministration of 400 mg sofosbuvir on Day 11, Period 2, with 200 mg [2 x 100 mg tablets] grazoprevir + 50 mg [1 x 50 mg tablet] elbasvir QD on Days 1 to 15, Period 2.
†Pseudo within-subject %CV = 100*Sqrt[(σ^2_A + σ^2_B - 2*σ_{AB})/2], where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
‡Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
§Median (Minimum, Maximum) reported for T_{max}.
‖Geometric mean and geometric coefficient of variation reported for apparent terminal $t_{½}$.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Subject Demographics

- Summary of subject disposition and characteristics can be found in **Table 3**

Table 3. Summary of subject disposition and characteristics

		Demographics
Entered		16
Completed		16
Male N (age range, years)		5 (22 – 52)
Female N (age range, years)		11 (26 – 51)
Height (mean and range, cm)		161.1 (142.0 – 188.0)
Weight (mean and range, kg)		70.1 (49.9 – 95.5)
BMI (mean and range, kg/m^2)		27.03 (20.25 – 31.57)
Race:	White	16
	Black or African American	0
Ethnicity:	Hispanic or Latino	15
	Not Hispanic or Latino	1

Safety and Tolerability

- A single dose of SOF alone, multiple doses of grazoprevir and elbasvir, and multiple doses of grazoprevir/elbasvir coadministered with a single oral dose of SOF were generally well tolerated in healthy male and female subjects
- No serious AEs or deaths were reported, and no subject was discontinued
- No clinically meaningful relationships were observed in clinical laboratory values, vital signs, or ECG safety parameter values

Five (5) subjects reported a total of 9 adverse events (7 mild and 2 moderate), 7 of which were considered by the investigator to be drug-related (to grazoprevir and elbasvir). The most common adverse event was abdominal pain, reported by 2 (12.5%) subjects. All adverse events were resolved by the end of the study.

Conclusions/Discussion

- Multiple-dose administration of 200 mg grazoprevir and 50 mg elbasvir daily with a single dose of SOF was generally well tolerated by healthy subjects in this study
- Coadministration of elbasvir and grazoprevir with SOF had no clinically meaningful effect on the pharmacokinetics of SOF and its metabolite GS-331007
- Taken together with the lack of potential for SOF to perpetrate a drug-drug interaction on grazoprevir or elbasvir, these results suggest that SOF, grazoprevir, and elbasvir may be coadministered without dose adjustment

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Disclosures

- This research was funded by Merck & Co., Inc., Kenilworth, NJ, USA.
- WLM, WWY, LC, PJ, XH, ZG, MM, H-PF, MI, and JRB are current employees of Merck & Co., Inc.
- DS, PA, CB-B, CB, DG, DA, and JB are current employees of Celerion.

Contact Information

William L. Marshall*
Merck & Co., Inc.
Kenilworth, NJ, USA
william.marshall@merck.com
*Corresponding author