No Meaningful Pharmacokinetic Interaction Between HCV Protease Inhibitor MK-5172 and Tenofovir or Raltegravir

WW Yeh,[1] IP Fraser,[1] L Caro,[1] J Talaty,[1] Z Guo,[1] H Davis,[1] SP Youngberg,[2] JR Butterton[1]

[1]Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA; [2]Celerion, Lincoln, NE, USA

Abstract

Background: MK-5172 is a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS3/4A protease that is being developed for the treatment of chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-co-infected patients. The present study evaluated the pharmacokinetic interactions and tolerability of MK-5172 coadministered either with tenofovir (TDF, an HIV nucleoside reverse transcriptase inhibitor) or raltegravir (RAL, an HIV integrase inhibitor) in healthy subjects.

Methodology: This was a 2-part, open-label, multiple-dose study in 24 healthy adult male and female volunteers, ages 19-55 years. Part 1: 12 subjects received oral doses of 300 mg TDF once daily on Days 1 to 7 in Period 1. After an 8 day washout, subjects received oral doses of 200 mg MK-5172 once daily on Days 1 to 7 in Period 2. In Period 3, subjects were coadministered 300 mg TDF and 200 mg MK-5172 once daily on Days 1 to 10. Part 2: 12 subjects received oral doses of 400 mg RAL twice daily on Days 1 to 4 in Period 1. After an 8 day washout, subjects received oral doses of 200 mg MK-5172 once daily on Days 1 to 7 in Period 2. In Period 3, subjects were coadministered 400 mg RAL twice daily and 200 mg MK-5172 once daily on Days 1 to 7. Plasma samples were collected for the PK assessment of MK-5172, TDF, and RAL.

Results: Co-administration of MK-5172 with either TDF or RAL was generally well-tolerated. In Part 1, multiple oral doses of MK-5172 slightly increased the steady-state $AUC_{0\text{-}24}$, C_{max}, and C_{24} of TDF with (TDF+MK-5172/TDF) geometric mean ratios (GMRs) [90% confidence intervals (CIs)] of 1.18 [1.09, 1.28], 1.14 [1.04, 1.25], and 1.24 [1.10, 1.39], respectively. Multiple oral doses of tenofovir did not meaningfully alter the steady-state $AUC_{0\text{-}24}$, C_{max}, or C_{24} of MK-5172 with (MK-5172+TDF/MK-5172) GMRs [90% CIs] of 0.86 [0.65, 1.12], 0.78 [0.51, 1.18], and 0.89 [0.78, 1.01], respectively. In Part 2, multiple oral doses of MK-5172 did not meaningfully alter the steady-state $AUC_{0\text{-}24}$, C_{max}, or C_{24} of RAL with (RAL+MK-5172/RAL) GMRs [90% CIs] of 1.43 [0.89, 2.3], 1.46 [0.78, 2.73], and 1.47 [1.08, 2.00], respectively. Multiple oral doses of RAL did not meaningfully alter the steady-state $AUC_{0\text{-}24}$, C_{max}, or C_{24} of MK-5172 with (MK-5172+RAL/MK-5172) GMRs [90% CIs] of 0.89 [0.72, 1.09], 0.85 [0.62, 1.16], and 0.90 [0.82, 0.99], respectively.

Conclusions: The coadministration of MK-5172 with either TDF or RAL in healthy volunteers did not result in clinically significant drug-drug interactions. These results suggest that no dose adjustments of MK-5172, TDF, or RAL are needed for coadministration in HCV/HIV coinfected patients and support further studies of MK-5172 with antiretroviral (ARV) regimens based on TDF and RAL in the co-infected population.

Background

- MK-5172 is a potent inhibitor of the hepatitis C virus (HCV) NS3/4A protease that is being developed as a once-daily treatment for chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-coinfected patients[1]
- Patients with chronic HCV infection and HIV coinfection have an increased risk of progression to cirrhosis or decompensated liver disease compared with HCV monoinfected patients
  - Antiretroviral therapy can slow the progression of liver disease by preserving/restoring immune function and reducing immune activation and inflammation, and therefore should be considered for all HIV/HCV-coinfected patients[2]
  - Tenofovir (TDF; a nucleoside reverse transcriptase inhibitor) and raltegravir (RAL; an HIV integrase strand transfer inhibitor) are components of initial antiretroviral regimens recommended for antiretroviral treatment (ART)-naive patients[3]
- In vitro data suggest that MK-5172 is metabolized by cytochrome P450 (CYP)3A4, and is also a potential inhibitor of uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1
  - RAL is primarily eliminated by glucuronidation mediated by the UGT1A1 enzymes[3]
  - TDF does not undergo hepatic metabolism via the CYP enzyme system[3]

Aim

- To evaluate the pharmacokinetic (PK) interactions and tolerability of MK-5172 when coadministered with TDF or RAL in healthy subjects

Patients and Methods

Subjects

- 24 healthy male and female subjects, 19 to 55 years old

Study Design

- This was a fixed-sequence, 3-treatment, 3-period, open-label study
- TDF and MK-5172 administration:
  - Period 1: TDF (300 mg once daily) for 7 days, followed by a washout period ≥5 days
  - Period 2: MK-5172 (200 mg once daily) for 7 days
  - Period 3: TDF (300 mg once daily) + MK-5172 (200 mg once daily) for 10 days
- RAL and MK-5172 administration:
  - Period 1: RAL (400 mg twice daily) for 4 days, followed by a washout period ≥3 days
  - Period 2: MK-5172 (200 mg once daily) for 7 days
  - Period 3: RAL (400 mg twice daily) + MK-5172 (200 mg once daily) for 7 days

Evaluations

- Plasma PK sampling schemes:
  - TDF and MK-5172
    - TDF: predose, and for 96 hours postdose on day 7 of period 1 and day 10 of period 3
    - MK-5172: predose, and for 24 hours postdose on day 7 of period 2, and for 96 hours postdose on day 10 of period 3
  - RAL and MK-5172
    - RAL: predose, and for 72 hours postdose on day 4 of period 1 and day 7 of period 3
    - MK-5172: predose, and for 24 hours postdose on day 7 of period 2, and for 72 hours postdose on day 7 of period 3
- Safety: adverse experiences (AEs), physical examination, vital signs, electrocardiogram (ECG), laboratory safety studies

Results

Patient Demographics

- Most subjects were white and non-Hispanic, with a mean age of 36 years (**Table 1**)

Table 1. Patient Characteristics

	Tenofovir and MK-5172 n = 12	Raltegravir and MK-5172 n = 12
Sex, n		
Male	9	7
Female	3	5
Race, n		
White	10	10
Black/African-American	2	1
Ethnicity, n		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	12
Age, y, mean (range)	36 (22, 50)	36 (21, 51)
BMI, kg/m^2, mean (range)	26.55 (20.29, 31.02)	26.09 (20.82, 31.38)

BMI = body mass index.

MK-5172 Pharmacokinetics

- The PK profile of MK-5172 was similar when administered alone, and in the presence of TDF (**Table 2**)
  - The mean MK-5172 area under the concentration-time curve ($AUC)_{0\text{-}24}$ was decreased by 14% following TDF coadministration
  - The $AUC_{0\text{-}24}$ geometric least-squares mean ratio (GMR) (90% confidence interval [CI]) for the TDF + MK-5172/MK-5172 comparison was 0.86 (0.65, 1.12)

Table 2. Statistical Comparison of Plasma Pharmacokinetics of MK-5172 Alone and in Combination With Tenofovir

Pharmacokinetic Parameter	MK-5172 Alone			MK-5172 + Tenofovir			Tenofovir + MK-5172/ MK-5172 Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$† (µM-h)	12	2.07	1.45, 2.96	12	1.77	1.26, 2.49	0.86	0.65, 1.12	36.895
C_{max}† (µM)	12	0.447	0.267, 0.747	12	0.348	0.202, 0.599	0.78	0.51, 1.18	56.689
C_{24}† (nM)	12	15.1	11.5, 19.8	12	13.4	9.95, 18.1	0.89	0.78, 1.01	17.277
T_{max}‡ (h)	12	3.00	2.00, 6.00	12	3.51	2.00, 6.00			
Apparent terminal half-life,§ $t_{½}$ (h)				12	26.85	33.80			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt($\beta\sigma A^2 + \sigma B^2$ - 2σAB/β), where σA² and σB² are the estimated variances on the log scale for the 2 treatment groups, and σAB is the corresponding estimated covariance, each obtained from the ANOVA 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 (percent geometric coefficient of variation) reported for terminal apparent $t_{½}$.

- The exposure of MK-5172 was similar whether or not it was coadministered with RAL, with a decrease in mean MK-5172 $AUC_{0\text{-}24}$ of 11% following RAL coadministration (**Table 3**)
  - The $AUC_{0\text{-}24}$ GMR (90% CI) for the RAL + MK-5172/MK-5172 comparison was 0.89 (0.72, 1.09)

Table 3. Statistical Comparison of Plasma Pharmacokinetics of MK-5172 Alone and in Combination With Raltegravir

Pharmacokinetic Parameter	MK-5172 Alone			MK-5172 + Raltegravir			MK-5172 + Raltegravir/ MK-5172 Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$† (µM-h)	11	2.78	1.71, 4.52	11	2.46	1.55, 3.92	0.89	0.72, 1.09	26.418
C_{max}† (µM)	11	0.653	0.334, 1.28	11	0.555	0.313, 0.984	0.85	0.62, 1.16	40.450
C_{24}† (nM)	11	17.8	12.9, 24.5	11	16.1	11.6, 22.2	0.90	0.82, 0.99	12.310
T_{max}‡ (h)	11	3.00	1.51, 4.02	11	3.01	2.00, 6.00			
Apparent terminal half-life,§ $t_{½}$ (h)				11	18.94	10.69			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt($\beta\sigma A^2 + \sigma B^2$ - 2σAB/β), where σA² and σB² are the estimated variances on the log scale for the 2 treatment groups, and σAB is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
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Tenofovir Pharmacokinetics

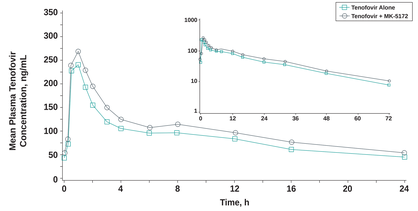
- The exposure of TDF was slightly higher when administered alone than when coadministered with MK-5172, with an increase in mean TDF $AUC_{0\text{-}24}$ of 18% following MK-5172 coadministration
  - The $AUC_{0\text{-}24}$ GMR (90% CI) for the TDF + MK-5172/TDF comparison was 1.18 (1.09, 1.28)
- The mean plasma concentration-time profile of TDF at and after C_{max} was slightly higher following coadministration with MK-5172 compared with the administration of TDF alone
  - The C_{max} GMR (90% CI) for the TDF + MK-5172/TDF comparison was 1.14 (1.04, 1.25)
- The overall shape of the profiles (including the very minor secondary peak at approximately 10 hours postdose) was similar for both treatment groups (**Table 4** and **Figure 1**)

Table 4. Statistical Comparison of Plasma Pharmacokinetics of Tenofovir (300 mg once daily) Alone and in Combination With MK-5172 (200 mg twice daily)

Pharmacokinetic Parameter	Tenofovir Alone			Tenofovir + MK-5172			Tenofovir + MK-5172/ Tenofovir Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$† (ng-h/mL)	12	2020	1750, 2330	12	2380	2000, 2840	1.18	1.09, 1.28	11.438
C_{max}† (ng/mL)	12	257	223, 296	12	293	246, 348	1.14	1.04, 1.25	13.029
C_{24}† (ng/mL)	12	43.1	36.6, 50.6	12	53.4	45.0, 63.3	1.24	1.10, 1.39	15.907
T_{max}‡ (h)	12	0.77	0.50, 1.50	12	1.01	0.52, 2.01			
Apparent terminal half-life,§ $t_{½}$ (h)	12	19.75	18.90	12	21.13	17.95			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt($\beta\sigma A^2 + \sigma B^2$ - 2σAB/β), where σA² and σB² are the estimated variances on the log scale for the 2 treatment groups, and σAB is the corresponding estimated covariance, each obtained from the ANOVA 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}.
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Figure 1. Mean plasma concentration-time profiles of tenofovir alone and following coadministration with MK-5172 (inset = semi-log scale).



Raltegravir Pharmacokinetics

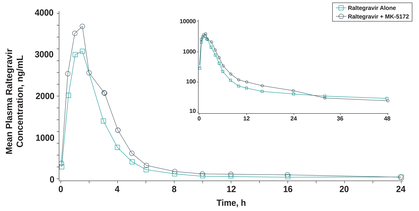
- The mean exposure of RAL was similar in the presence of MK-5172 compared with when administered alone, with an increase in mean RAL $AUC_{0\text{-}12}$ of 43% following MK-5172 co-administration (**Table 5**)
  - The $AUC_{0\text{-}12}$ GMR (90% CI) for the RAL + MK-5172/RAL comparison was 1.43 (0.89, 2.30)
- The mean C_{12} of RAL was increased by 47% in the presence of MK-5172 compared with when administered alone
  - The C_{12} GMR (90% CI) for the RAL + MK-5172/RAL comparison was 1.47 (1.085, 1.998)
  - The apparent increase in RAL C_{12} was associated with a large variability in RAL concentration observed at this time point
- The mean plasma RAL concentration time profile was similar in the presence of MK-5172 compared with when administered alone, with slightly higher peak values at and after C_{max} (**Table 5** and **Figure 2**)

Table 5. Statistical Comparison of Plasma Pharmacokinetics of Raltegravir (400 mg twice daily) Alone and in Combination With MK-5172 (200 mg twice daily)

Pharmacokinetic Parameter	Raltegravir Alone			Raltegravir + MK-5172			Raltegravir + MK-5172/ Raltegravir Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}12}$† (ng-hr/mL)	11	6.07	3.18, 11.6	11	8.67	4.86, 15.5	1.43	0.89, 2.30	61.385
C_{max}† (ng/mL)	11	1.84	0.809, 4.18	11	2.69	1.30, 5.54	1.46	0.78, 2.73	80.814
C_{12}† (ng/mL)	11	54.0	36.9, 79.0	11	79.4	48.8, 129	1.47	1.085, 1.998	39.497
T_{max}‡ (h)	11	1.00	0.50, 4.00	11	1.50	0.00, 4.01			
Apparent terminal half-life,§ $t_{½}$ (h)	10¶	12.44	86.97	11	12.70	118.51			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt($\beta\sigma A^2 + \sigma B^2$ - 2σAB/β), where σA² and σB² are the estimated variances on the log scale for the 2 treatment groups, and σAB is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
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§Geometric mean (percent geometric coefficient of variation) reported for terminal apparent $t_{½}$.
¶Data from 1 subject in period 1 excluded because it was considered an outlier.

Figure 2. Mean plasma concentration-time profiles of raltegravir alone and following coadministration with MK-5172 (inset = semi-log scale).



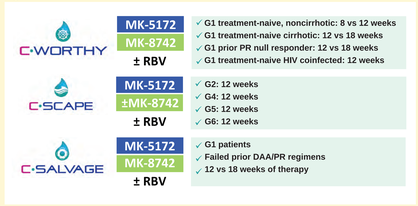
Safety and Tolerability

- Multiple dose MK-5172 (200 mg once daily) was generally well tolerated when administered alone or in combination with TDF or RAL in healthy subjects
- 23 subjects completed the study: 1 subject in the RAL arm was discontinued due to a positive urine drug screen test
- 11 subjects reported a total of 41 mild AEs
  - The most common AEs were:
    - Diarrhea (MK-5172, n = 1; TDF, n = 1; RAL, n = 1; TDF + MK-5172, n = 1)
    - Dyspepsia (TDF, n = 1; RAL + MK-5172, n = 2)
    - Headache (MK-5172, n = 1; TDF, n = 1; RAL, n = 1)
  - All other AEs were each reported by single subjects
  - MK-5172 treatment-related AEs included upper abdominal pain (MK-5172 alone), and disturbance in attention, dry mouth, and dysgeusia (each reported by single subjects receiving TDF + MK-5172)
- There were no consistent treatment-related changes in laboratory values, vital signs, or ECG parameters
- There were no deaths or serious AEs, and no subject was discontinued because of an AE

Conclusions

- The coadministration of MK-5172 with either TDF or RAL in healthy volunteers did not result in clinically significant drug-drug interactions
- These results suggest that no dose adjustments of MK-5172, TDF, or RAL are needed for coadministration in HCV/HIV-coinfected patients
- These data support further studies of MK-5172 with antiretroviral regimens based on TDF and RAL in HIV/HCV-coinfected patients
- Ongoing phase 2b studies with MK-5172 (**Figure 3**) will provide additional data regarding the efficacy and safety of this compound in the treatment of HCV infection

Figure 3. Phase 2b studies with MK-5172.



DAA = direct-acting antiviral agent; G = genotype; PR = peginterferon/ribavirin; RBV = ribavirin.

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3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed January 30, 2014.

Disclosures

WWY, IPF, LC, JT, ZG, HD, and JRB are current employees of Merck & Co., Inc., Whitehouse Station, NJ. SPY was employed by Celerion, Inc., Lincoln, NE. Medical writing and editorial assistance was provided by Tim Ibbotson, PhD, and Beth McMahon-Wise, PhD, of ApotheCom. This assistance was funded by Merck & Co., Inc., Whitehouse Station, NJ. This study was funded by Merck & Co., Inc., Whitehouse Station, NJ.

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  - Period 1: RAL (400 mg twice daily) for 4 days, followed by a washout period ≥3 days
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  - The AUC_{0-24} geometric least-squares mean ratio (GMR) (90% confidence interval [CI]) for the TDF + MK-5172/MK-5172 comparison was 0.86 (0.65, 1.12)

Table 2. Statistical Comparison of Plasma Pharmacokinetics of MK-5172 Alone and in Combination With Tenofovir

Pharmacokinetic Parameter	MK-5172 Alone			MK-5172 + Tenofovir			Tenofovir + MK-5172/ MK-5172 Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}† (μM·h)	12	2.07	1.45, 2.96	12	1.77	1.26, 2.49	0.86	0.65, 1.12	36.895
C_{max}† (μM)	12	0.447	0.267, 0.747	12	0.348	0.202, 0.599	0.78	0.51, 1.18	56.689
C_{24}† (nM)	12	15.1	11.5, 19.8	12	13.4	9.95, 18.1	0.89	0.78, 1.01	17.277
T_{max}‡ (h)	12	3.00	2.00, 6.00	12	3.51	2.00, 6.00			
Apparent terminal half-life,¶ $t_{½}$ (h)				12	26.85	33.80			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt[(σA^2 + σB^2 - 2σAB)/2], where σA^2 and σB^2 are the estimated variances on the log scale for the 2 treatment groups, and σAB is the corresponding estimated covariance, each obtained from the ANOVA 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 (percent geometric coefficient of variation) reported for terminal apparent $t_{½}$.

- The exposure of MK-5172 was similar whether or not it was coadministered with RAL, with a decrease in mean MK-5172 AUC_{0-24} of 11% following RAL coadministration (**Table 3**)
  - The AUC_{0-24} GMR (90% CI) for the RAL + MK-5172/MK-5172 comparison was 0.89 (0.72, 1.09)

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Table 3. Statistical Comparison of Plasma Pharmacokinetics of MK-5172 Alone and in Combination With Raltegravir

Pharmacokinetic Parameter	MK-5172 Alone			MK-5172 + Raltegravir			MK-5172 + Raltegravir/ MK-5172 Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}† (µM·h)	11	2.78	1.71, 4.52	11	2.46	1.55, 3.92	0.89	0.72, 1.09	26.418
C_{max}† (µM)	11	0.653	0.334, 1.28	11	0.555	0.313, 0.984	0.85	0.62, 1.16	40.450
C_{24}† (nM)	11	17.8	12.9, 24.5	11	16.1	11.6, 22.2	0.90	0.82, 0.99	12.310
T_{max}‡ (h)	11	3.00	1.51, 4.02	11	3.01	2.00, 6.00			
Apparent terminal half-life,¶ $t_{½}$ (h)				11	18.94	10.69			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt[(σA^2 + σB^2 - 2σAB)/2], where σA^2 and σB^2 are the estimated variances on the log scale for the 2 treatment groups, and σAB is the corresponding estimated covariance, each obtained from the ANOVA 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 (percent geometric coefficient of variation) reported for terminal apparent $t_{½}$.

Tenofovir Pharmacokinetics

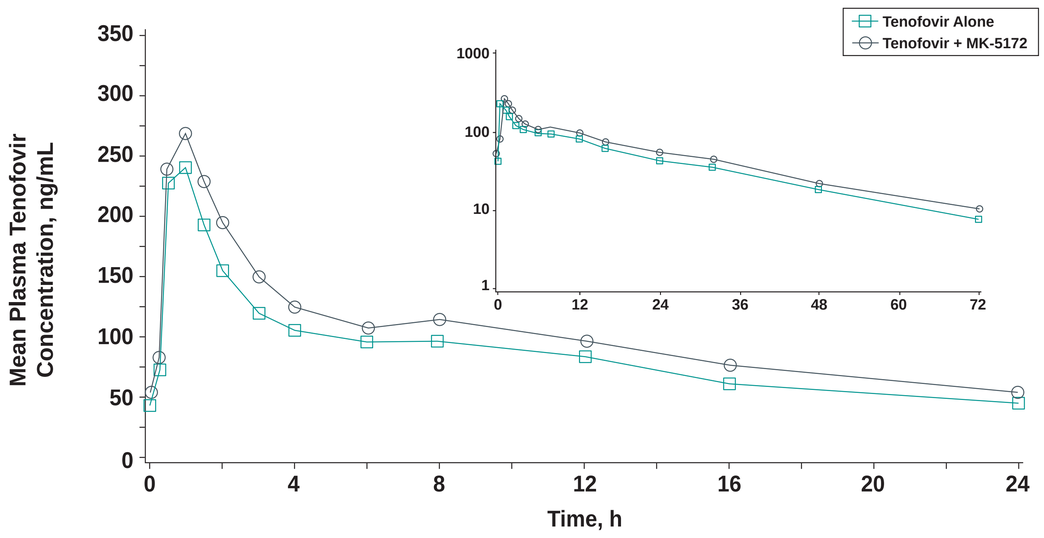
- The exposure of TDF was slightly higher when administered alone than when coadministered with MK-5172, with an increase in mean TDF AUC_{0-24} of 18% following MK-5172 coadministration
  - The AUC_{0-24} GMR (90% CI) for the TDF + MK-5172/TDF comparison was 1.18 (1.09, 1.28)
- The mean plasma concentration-time profile of TDF at and after C_{max} was slightly higher following coadministration with MK-5172 compared with the administration of TDF alone
  - The C_{max} GMR (90% CI) for the TDF + MK-5172/TDF comparison was 1.14 (1.04, 1.25)
- The overall shape of the profiles (including the very minor secondary peak at approximately 10 hours postdose) was similar for both treatment groups (**Table 4** and **Figure 1)**

Table 4. Statistical Comparison of Plasma Pharmacokinetics of Tenofovir (300 mg once daily) Alone and in Combination With MK-5172 (200 mg twice daily)

Pharmacokinetic Parameter	Tenofovir Alone			Tenofovir + MK-5172			Tenofovir + MK-5172/ Tenofovir Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}† (ng·h/mL)	12	2020	1750, 2330	12	2380	2000, 2840	1.18	1.09, 1.28	11.438
C_{max}† (ng/mL)	12	257	223, 296	12	293	246, 348	1.14	1.04, 1.25	13.029
C_{24}† (ng/mL)	12	43.1	36.6, 50.6	12	53.4	45.0, 63.3	1.24	1.10, 1.39	15.907
T_{max}‡ (h)	12	0.77	0.50, 1.50	12	1.01	0.52, 2.01			
Apparent terminal half-life,¶ $t_{½}$ (h)	12	19.75	18.90	12	21.13	17.95			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt[(σA^2 + σB^2 - 2σAB)/2], where σA^2 and σB^2 are the estimated variances on the log scale for the 2 treatment groups, and σAB is the corresponding estimated covariance, each obtained from the ANOVA 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 (percent geometric coefficient of variation) reported for terminal apparent $t_{½}$.

Figure 1. Mean plasma concentration-time profiles of tenofovir alone and following coadministration with MK-5172 (inset = semi-log scale).



Raltegravir Pharmacokinetics

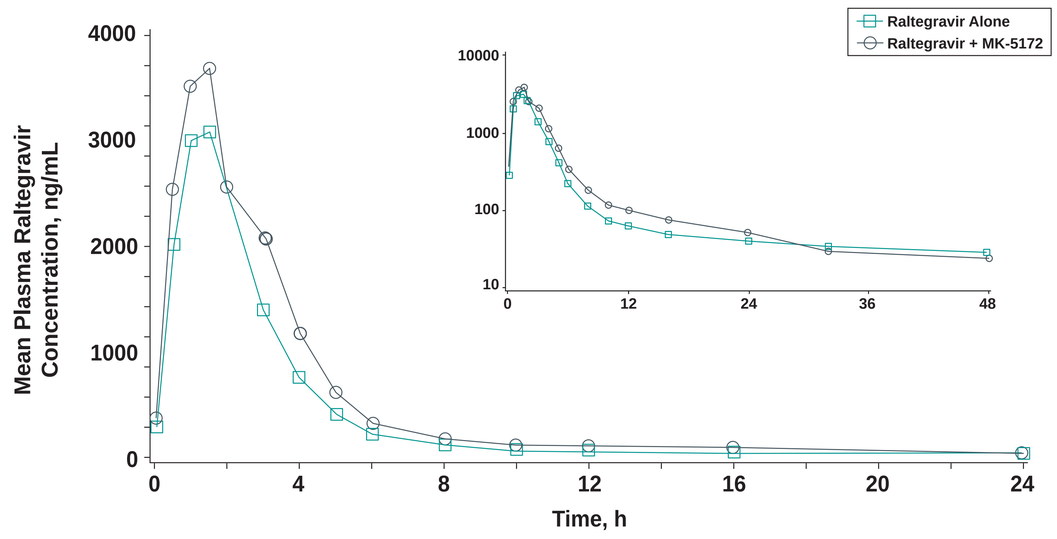
- The mean exposure of RAL was similar in the presence of MK-5172 compared with when administered alone, with an increase in mean RAL AUC_{0-12} of 43% following MK-5172 co-administration (**Table 5**)
  - The AUC_{0-12} GMR (90% CI) for the RAL + MK-5172/RAL comparison was 1.43 (0.89, 2.30)
- The mean C_{12} of RAL was increased by 47% in the presence of MK-5172 compared with when administered alone
  - The C_{12} GMR (90% CI) for the RAL + MK-5172/RAL comparison was 1.47 (1.085, 1.998)
  - The apparent increase in RAL C_{12} was associated with a large variability in RAL concentration observed at this time point
- The mean plasma RAL concentration time profile was similar in the presence of MK-5172 compared with when administered alone, with slightly higher peak values at and after C_{max} (**Table 5** and **Figure 2**)

Table 5. Statistical Comparison of Plasma Pharmacokinetics of Raltegravir (400 mg twice daily) Alone and in Combination With MK-5172 (200 mg twice daily)

Pharmacokinetic Parameter	Raltegravir Alone			Raltegravir + MK-5172			Raltegravir + MK-5172/ Raltegravir Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-12}† (ng·hr/mL)	11	6.07	3.18, 11.6	11	8.67	4.86, 15.5	1.43	0.89, 2.30	61.385
C_{max}† (ng/mL)	11	1.84	0.809, 4.18	11	2.69	1.30, 5.54	1.46	0.78, 2.73	80.814
C_{12}† (ng/mL)	11	54.0	36.9, 79.0	11	79.4	48.8, 129	1.47	1.085, 1.998	39.497
T_{max}‡ (h)	11	1.00	0.50, 4.00	11	1.50	0.00, 4.01			
Apparent terminal half-life,¶ $t_{½}$ (h)	10§	12.44	86.97	11	12.70	118.51			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt[(σA^2 + σB^2 - 2σAB)/2], where σA^2 and σB^2 are the estimated variances on the log scale for the 2 treatment groups, and σAB is the corresponding estimated covariance, each obtained from the ANOVA 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 (percent geometric coefficient of variation) reported for terminal apparent $t_{½}$.
§Data from 1 subject in period 1 excluded because it was considered an outlier.

Figure 2. Mean plasma concentration-time profiles of raltegravir alone and following coadministration with MK-5172 (inset = semi-log scale).



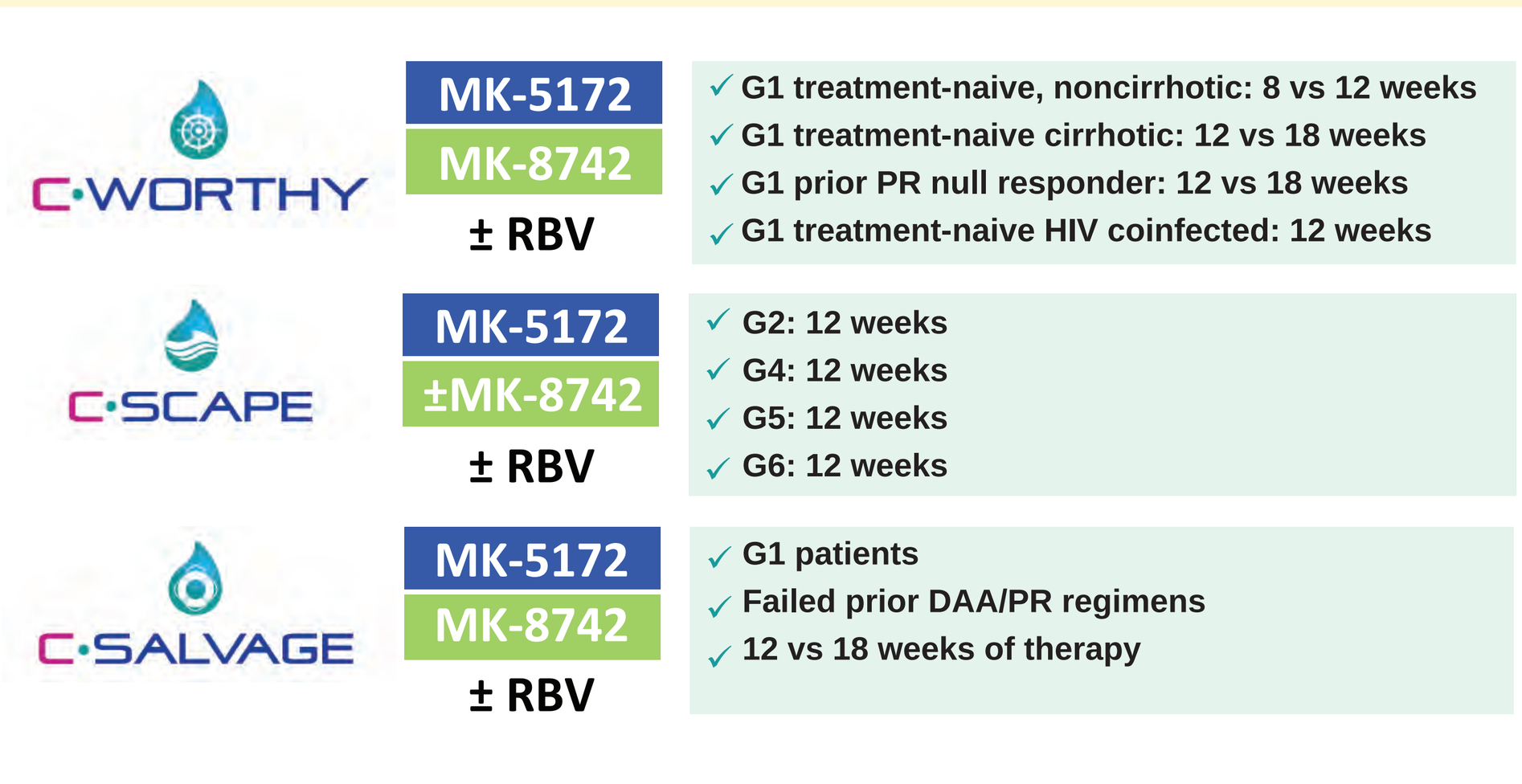
Safety and Tolerability

- Multiple dose MK-5172 (200 mg once daily) was generally well tolerated when administered alone or in combination with TDF or RAL in healthy subjects
- 23 subjects completed the study: 1 subject in the RAL arm was discontinued due to a positive urine drug screen test
- 11 subjects reported a total of 41 mild AEs
  - The most common AEs were:
    - Diarrhea (MK-5172, n = 1; TDF, n = 1; RAL, n = 1; TDF + MK-5172, n = 1)
    - Dyspepsia (TDF, n = 1; RAL + MK-5172, n = 2)
    - Headache (MK-5172, n = 1; TDF, n = 1; RAL, n = 1)
  - All other AEs were each reported by single subjects
  - MK-5172 treatment-related AEs included upper abdominal pain (MK-5172 alone), and disturbance in attention, dry mouth, and dysgeusia (each reported by single subjects receiving TDF + MK-5172)
- There were no consistent treatment-related changes in laboratory values, vital signs, or ECG parameters
- There were no deaths or serious AEs, and no subject was discontinued because of an AE

Conclusions

- The coadministration of MK-5172 with either TDF or RAL in healthy volunteers did not result in clinically significant drug-drug interactions
- These results suggest that no dose adjustments of MK-5172, TDF, or RAL are needed for coadministration in HCV/HIV-coinfected patients
- These data support further studies of MK-5172 with antiretroviral regimens based on TDF and RAL in HIV/HCV-coinfected patients
- Ongoing phase 2b studies with MK-5172 (**Figure 3**) will provide additional data regarding the efficacy and safety of this compound in the treatment of HCV infection

Figure 3. Phase 2b studies with MK-5172.



DAA = direct-acting antiviral agent; G = genotype; PR = peginterferon/ribavirin; RBV = ribavirin.

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Disclosures

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