Pharmacokinetic Interactions Between the HCV NS5A Inhibitor MK-8742 and Tenofovir (TDF), Raltegravir (RAL), and Efavirenz (EFV)

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Abstract

Background: MK-8742, an inhibitor of the hepatitis C virus (HCV) NS5A protein, is being developed for the treatment of HCV infection. HCV infection is a major cause of morbidity and mortality in patients coinfected with human immunodeficiency virus-1 (HIV) and HCV. This study evaluated the pharmacokinetic interactions and safety of MK-8742 coadministered with either TDF, RAL, or EFV in healthy subjects.

Methodology: This was a 3-part, open-label, fixed-sequence study in 30 healthy adult male and female volunteers, ages 19–55 years. In Part 1, 10 subjects received oral doses of 300 mg TDF once daily for 7 days followed by a ≥5-day washout, 50 mg MK-8742 once daily for 8 days, and then 50 mg MK-8742 and 300 mg TDF coadministered once daily for 7 days. In Part 2, 10 subjects received a single oral dose of 400 mg RAL followed by a ≥3-day washout, a single oral dose of 50 mg MK-8742 followed by a ≥7-day washout, and then a single oral dose of 400 mg RAL coadministered with a single oral dose of 50 mg MK-8742. In Part 3, 10 subjects received oral doses of 50 mg MK-8742 once daily for 8 days followed by a 7-day washout, oral doses of 600 mg EFV once daily for 14 days, and then oral doses of 50 mg MK-8742 and 600 mg EFV coadministered once daily for 8 days. Safety assessments included electrocardiograms, vital signs, clinical laboratory tests, physical examination, and adverse event monitoring.

Results: Coadministration of MK-8742 with either TDF, RAL, or EFV was safe and generally well-tolerated. In Part 1, multiple oral doses of MK-8742 increased the steady-state $AUC_{0\text{-}24}$ of TDF with (TDF+MK-8742/TDF) geometric mean ratio (GMR) [90% confidence intervals (CIs)] of 1.34 [1.23, 1.47]. Multiple oral doses of TDF did not meaningfully alter the steady-state $AUC_{0\text{-}24}$ of MK-8742 with (MK-8742+TDF/MK-8742) GMR of 0.93 [0.82, 1.05]. In Part 2, coadministration of MK-8742 did not alter the steady-state $AUC_{0\text{-}\infty}$ of RAL with (RAL+MK-8742/RAL) GMR of 1.02 [0.81, 1.27]. Coadministration of RAL did not alter the steady-state $AUC_{0\text{-}\infty}$ MK-8742 with (MK-8742+RAL/MK-8742) GMR of 0.81 [0.57, 1.17]. In Part 3, multiple oral doses of EFV decreased the $AUC_{0\text{-}24}$ of MK-8742 with (MK-8742+EFV/MK-8742) GMR of 0.46 [0.36, 0.59]. Multiple oral doses of MK-8742 did not meaningfully change the steady-state $AUC_{0\text{-}24}$ of EFV with (EFV+MK-8742/EFV) GMR of 0.82 [0.78, 0.86].

Conclusions: MK-8742 concentrations decreased following coadministration with EFV, likely as a result of CYP3A4 induction by EFV. Coadministration of MK-8742 and either RAL or TDF in healthy volunteers did not result in clinically meaningful drug-drug interactions.

Background

- MK-8742, a potent inhibitor of the hepatitis C virus (HCV) NS5A, is being developed as a once-daily treatment for chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-coinfected patients
  - A previous ketoconazole drug-drug interaction study has demonstrated that MK-8742 is a CYP3A4 substrate in vivo
  - MK-8742 is also a substrate of P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro
- Efavirenz (EFV; a non-nucleoside reverse transcriptase inhibitor), raltegravir (RAL; an integrase strand transfer inhibitor), and tenofovir (TDF; a nucleoside reverse transcriptase inhibitor) are recommended first-line therapies for treatment of HIV infection in HIV monoinfected and HIV/HCV-coinfected patients[1]
  - EFV is metabolized by CYP450 3A isoenzymes and is a substrate of CYP2B6[1]
    - It is a mixed inducer and inhibitor, but primarily induces CYP3A and 2B6
  - RAL is primarily eliminated by glucuronidation mediated by the UGT1A1 enzymes[1]
  - TDF does not undergo hepatic metabolism via the CYP enzyme system[1]

Aim

- To evaluate the pharmacokinetic (PK) interactions, safety, and tolerability of MK-8742 when coadministered with TDF, RAL, or EFV in healthy subjects

Patients and Methods

Subjects

- 30 healthy, nonsmoking, adult subjects were enrolled, with 10 subjects enrolled in each study part (a minimum of 4 female patients were included in each part)

Study Design

- A 3-part, fixed-sequence, 3-treatment, 3-period, open-label study to evaluate the pharmacokinetic interactions between MK-8742 and TDF, RAL, and EFV
- Treatments
  - Part 1: TDF and MK-8742 administration
    - Period 1: TDF (300 mg once daily) for 7 days, then washout for ≥5 days
    - Period 2: MK-8742 (50 mg once daily) for 8 days
    - Period 3: TDF (300 mg once daily) + MK-8742 (50 mg once daily) for 7 days
  - Part 2: RAL and MK-8742 administration
    - Period 1: RAL (single dose 400 mg), then washout for ≥3 days
    - Period 2: MK-8742 (single dose 50 mg), then washout for ≥7 days
    - Period 3: RAL (single dose 400 mg) + MK-8742 (single dose 50 mg)
  - Part 3: MK-8742 and EFV administration
    - Period 1: MK-8742 (50 mg once daily) for 8 days, then washout for ≥7 days
    - Period 2: EFV (600 mg once daily) for 14 days
    - Period 3: MK-8742 (50 mg once daily) + EFV (600 mg once daily) for 8 days

Evaluations

- PK parameters
  - Area under the concentration-time curve ($AUC)_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, maximum concentration (C_{max}), trough concentration (C_{trough}), C_{12}, C_{24}, time to maximum concentration (T_{max}), and apparent terminal half-life ($t_{½}$)
- PK blood sampling scheme
  - MK-8742: predose, and up to 72 hours postdose in part 2 (periods 2 and 3), and up to 24 hours postdose in parts 1 (periods 2 and 3) and 3 (periods 1 and 3)
  - TDF: predose, and up to 24 hours postdose in periods 1 and 3 of part 1
  - RAL: predose, and up to 48 hours postdose in periods 1 and 3 of part 2
  - EFV: predose, and up to 24 hours postdose in periods 2 and 3 in part 3
- Safety: adverse event (AE) monitoring, physical examination, vital signs, electrocardiogram (ECG), and laboratory safety studies

Results

Patient Demographics

- In all 3 parts of the study, most patients were white and non-Hispanic/non-Latino (**Table 1**)

Table 1. Patient Characteristics

	TDF and MK-8742 n = 10	RAL and MK-8742 n = 10	EFV and MK-8742 n = 10
Sex, n			
Male	6	6	5
Female	4	4	5
Race, n			
White	9	7	8
Other	1	3	2
Ethnicity, n			
Hispanic/Latino	1	2	1
Non-Hispanic/non-Latino	9	8	9
Age, y, mean (range)	33 (21, 53)	29 (20, 47)	37 (23, 53)
BMI, kg/m^2, mean (range)	25.18 (19.61, 31.45)	26.28 (20.01, 31.84)	26.45 (21.95, 31.39)

BMI = body mass index; EFV = efavirenz; RAL = raltegravir; TDF = tenofovir.

Pharmacokinetics

MK-8742

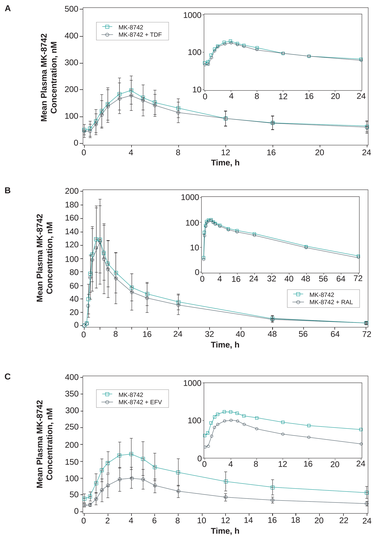
- Coadministration of MK-8742 with TDF or RAL did not meaningfully alter the $AUC_{0\text{-}24}$ or $AUC_{0\text{-}\infty}$ of MK-8742 (**Table 2** and **Figure 1**)
  - There was a 7% and 19% drop in the exposure of MK-8742 when coadministered with TDF and RAL, respectively
- Coadministration of MK-8742 with EFV decreased the $AUC_{0\text{-}24}$ of MK-8742 by approximately 54%
  - The MK-8742 $AUC_{0\text{-}24}$ geometric least-squares mean ratio (GMR) (90% confidence interval [CI]) for the comparison of MK-8742 + EFV versus MK-8742 alone was 0.46 (0.36, 0.59)
  - The 90% CI was not contained within [0.50, 2.00], the prespecified limits designating lack of a clinically meaningful change; therefore, the primary hypothesis that the $AUC_{0\text{-}24}$ of MK-8742 in the presence of EFV is similar to that of MK-8742 alone was not supported

Table 2. Statistical Comparison of Area Under the Plasma Concentration Time Curve of MK-8742 Alone and in Combination With TDF, RAL, or EFV

	Pharmacokinetic Parameter	MK-8742 + Drug/ MK-8742 Alone		Pseudo Within Subject %CV*	MK-8742 Alone			MK-8742 + Drug			
		GMR	90% CI		N	GM	95% CI	Drug	N	GM	95% CI
Part 1 (TDF)	$AUC_{0\text{-}24}$† (μM·h)	0.93	0.82, 1.05	14.657	10	2.45	2.05, 2.94	Tenofovir	10	2.28	1.84, 2.81
Part 2 (RAL)	$AUC_{0\text{-}\infty}$† (μM·h)	0.81	0.57, 1.17	43.837	10	2.19	1.69, 2.83	Raltegravir	10	1.78	1.14, 2.77
Part 3 (EFV)	$AUC_{0\text{-}24}$† (μM·h)	0.46	0.36, 0.59	20.528	10	2.21	1.76, 2.77	Efavirenz	7‡	1.01	0.665, 1.54

AE = adverse event; ANOVA = analysis of variance; AUC = area under the concentration-time curve; CI = confidence interval; EFV = efavirenz; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; RAL = raltegravir; TDF = tenofovir.
*Pseudo within-subject %CV = 100 × $Sqrt(\alpha A^2 + \alpha B^2 - 2\alpha AB)/2$, where αA^2 and αB^2 are the estimated variances on the log scale for the 2 treatment groups, and αAB 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.
‡3 subjects discontinued treatment because of efavirenz-related AEs.

Figure 1. Plasma concentration time profiles for MK-8742 alone and in the presence of (A) tenofovir (TDF), (B) raltegravir (RAL), and (C) efavirenz (EFV).



TDF Pharmacokinetics

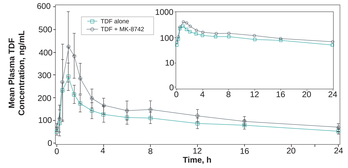
- Coadministration of TDF with MK-8742 increased the plasma $AUC_{0\text{-}24}$ and C_{max} of TDF by approximately 34% and 47%, respectively (**Table 3** and **Figure 2**)

Table 3. Statistical Comparison of Plasma Pharmacokinetics of Tenofovir Alone and in Combination With MK-8742

Pharmacokinetic parameter	TDF Alone			TDF + MK-8742			TDF + MK-8742/TDF Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$† (μg·h/mL)	10	2.36	2.01, 2.77	10	3.17	2.71, 3.71	1.34	1.23, 1.47	10.643
C_{max}† (ng/mL)	10	302	247, 368	10	442	359, 545	1.47	1.32, 1.63	12.879
C_{24}† (ng/mL)	10	51.7	43.0, 62.1	10	66.5	55.3, 79.9	1.29	1.18, 1.41	10.939
T_{max}‡ (h)	10	1.00	0.50, 1.00	10	1.01	0.51, 1.51			

ANOVA = analysis of variance; AUC = area under the concentration-time 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; TDF = tenofovir.
*Pseudo within-subject %CV = 100 × $Sqrt(\alpha A^2 + \alpha B^2 - 2\alpha AB)/2$, where αA^2 and αB^2 are the estimated variances on the log scale for the 2 treatment groups, and αAB 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}.

Figure 2. Plasma concentration time profiles for tenofovir (TDF) alone and in the presence MK-8742.



RAL Pharmacokinetics

- Coadministration of a single dose of RAL and a single dose of MK-8742 did not meaningfully alter the C_{12} or $AUC_{0\text{-}\infty}$ of RAL (**Table 4** and **Figure 3**)

Table 4. Statistical Comparison of Plasma Pharmacokinetics of Raltegravir Alone and in Combination With MK-8742

Pharmacokinetic Parameter	RAL Alone			RAL + MK-8742			RAL + MK-8742/RAL Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}\infty}$† (μg·h/mL)	10	5.35	3.05, 9.40	10	5.45	3.18, 9.35	1.02	0.81, 1.27	27.207
C_{max}† (ng/mL)	10	1.53	0.806, 2.90	10	1.67	0.839, 3.34	1.09	0.83, 1.44	33.755
C_{12}† (ng/mL)	10	42.7	30.4, 60.1	10	42.4	31.2, 57.5	0.99	0.80, 1.22	25.475
T_{max}‡ (h)	10	2.50	0.50, 5.00	10	1.76	0.51, 5.00			
Apparent terminal $t_{½}$ (h)¶	10	8.56	101.36	10	9.23	53.66			

ANOVA = analysis of variance; AUC = area under the concentration-time curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; RAL = raltegravir; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × $Sqrt(\alpha A^2 + \alpha B^2 - 2\alpha AB)/2$, where αA^2 and αB^2 are the estimated variances on the log scale for the 2 treatment groups, and αAB is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
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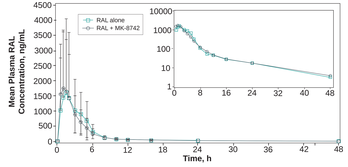
‡Median (minimum, maximum) reported for T_{max}.
¶Geometric mean, geometric coefficient of variation reported for apparent terminal $t_{½}$.

Figure 3. Plasma concentration time profiles for raltegravir (RAL) alone and in the presence MK-8742.



EFV Pharmacokinetics

- Concomitant administration of EFV and MK-8742 did not meaningfully alter the plasma $AUC_{0\text{-}24}$ of EFV (**Table 5** and **Figure 4**)
  - The C_{max} for EFV was reduced by 26% in the presence of MK-8742
  - There was an 18% decrease in the $AUC_{0\text{-}24}$ of EFV in the presence of MK-8742; however, the 90% CI (0.78, 0.86) remained within the protocol-specified limits for clinical significance of [0.70, 1.43]

Table 5. Statistical Comparison of Plasma Pharmacokinetics of Efavirenz Alone and in Combination With MK-8742

Pharmacokinetic Parameter	EFV Alone			EFV + MK-8742			EFV + MK-8742 / EFV Alone		Pseudo Within Subject %CV*
	N‡	GM	95% CI	N‡	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$ (μg·h/mL)	7	64.9	56.1, 75.0	7	53.0	46.7, 60.2	0.82	0.78, 0.86	4.465
C_{max}† (μg/mL)	7	4.46	3.85, 5.15	7	3.30	3.04, 3.58	0.74	0.67, 0.82	9.720
C_{24}† (ng/mL)	7	1910	1620, 2250	7	1740	1520, 1990	0.91	0.87, 0.96	4.734
T_{max}§ (h)	7	3.10	2.00, 5.00	7	4.00	2.00, 5.00			

AE = adverse event; ANOVA = analysis of variance; AUC = area under the concentration-time curve; C_{max} = maximum concentration; CI = confidence interval; EFV = efavirenz; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × $Sqrt(\alpha A^2 + \alpha B^2 - 2\alpha AB)/2$, where αA^2 and αB^2 are the estimated variances on the log scale for the 2 treatment groups, and αAB 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.
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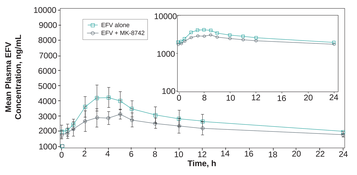
§3 subjects discontinued treatment because of efavirenz-related AEs.

Figure 4. Plasma concentration time profiles for efavirenz (EFV) alone and in the presence MK-8742.



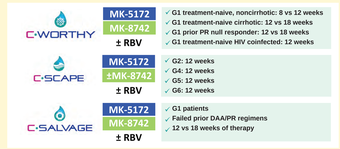
Safety and Tolerability

- No deaths or serious AEs were reported. There were also no consistent treatment-related changes in laboratory values, vital signs, or ECG safety parameters
- TDF and MK-8742
  - All 10 subjects completed the study. Nine subjects reported a total of 28 AEs, 9 of which were considered related to study drugs (MK-8742 alone, n = 8; MK-8742 + TDF, n = 1)
  - All AEs were mild to moderate intensity
  - The most commonly reported AEs were headache (n = 4), diarrhea (n = 3), and abdominal pain (n = 2)
- RAL and MK-8742
  - All 10 subjects completed the study. Two mild AEs were reported
  - One subject reported 2 AEs of fatigue both of which were considered to be related to MK-8742 (MK-8742 alone, n = 1; MK-8742 + RAL, n = 1)
- EFV and MK-8742
  - Three subjects were discontinued because of drug-related AEs following administration of EFV alone (drug eruption, n = 2; drug eruption and generalized maculopapular rash, n = 1).
    - All AEs were mild in intensity, with the exception of a renal colic AE that was severe and this AE was not considered drug related
    - Ten subjects reported a total of 37 clinical AEs, 25 of which were considered to be related to study drugs (EFV, n = 23; MK-8742, n = 2)
    - The most commonly reported AEs were drug eruption, dizziness, and feeling intoxicated (n = 3 each, all in subjects receiving EFV alone)

Summary and Conclusions

- MK-8742 concentrations decreased following coadministration with EFV, possibly as a result of CYP3A4 induction by EFV
- Coadministration of MK-8742 with either RAL or TDF did not result in clinically meaningful drug-drug interactions
  - No dose adjustments would be required by patients with HCV/HIV coinfection undergoing therapy with MK-8742 and TDF or RAL
- Coadministration of MK-8742 with TDF, RAL, or EFV was generally well tolerated
- Ongoing phase 2b studies with MK-8742 (**Figure 5**) will provide additional data regarding the efficacy and safety of this compound in the treatment of HCV infection

Figure 5. Phase 2b studies with MK-8742.



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

Reference

1. 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

BY had a financial relationship within the last 12 months relevant to the presentation with Merck & Co., Inc., Whitehouse Station, NJ. WM, PJ, WY, XH, and JRB are current employees of Merck & Co. Inc., Whitehouse Station, NJ. USA. YZ, JM, and EM were employees of Merck & Co. Inc., Whitehouse Station, NJ, USA at the time this study was conducted. EM is a current employee of Stryker Corporation, Mahwah, PA, USA. This study was funded by Merck & Co., Inc., Whitehouse Station, NJ. Medical writing and editorial assistance was provided by Tim Bilotkoski, PhD, and Barb McMahon-Wise, PhD, of AptoheCom. This assistance was funded by Merck & Co., Inc., Whitehouse Station, NJ.

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Results: Coadministration of MK-8742 with either TDF, RAL, or EFV was safe and generally well-tolerated. In Part 1, multiple oral doses of MK-8742 increased the steady-state AUC_{0-24} of TDF with (TDF+MK-8742/TDF) geometric mean ratio (GMR) [90% confidence intervals (CIs)] of 1.34 [1.23, 1.47]. Multiple oral doses of TDF did not meaningfully alter the steady-state AUC_{0-24} of MK-8742 with (MK-8742+TDF/MK-8742) GMR of 0.93 [0.82, 1.05]. In Part 2, coadministration of MK-8742 did not alter the steady-state $AUC_{0-\infty}$, of RAL with (RAL+MK-8742/RAL) GMR of 1.02 [0.81, 1.27]. Coadministration of RAL did not alter the steady-state $AUC_{0-\infty}$ MK-8742 with (MK-8742+RAL/MK-8742) GMR of 0.81 [0.57, 1.17]. In Part 3, multiple oral doses of EFV decreased the AUC_{0-24} of MK-8742 with (MK-8742+EFV/MK-8742) GMR of 0.46 [0.36, 0.59]. Multiple oral doses of MK-8742 did not meaningfully change the steady-state AUC_{0-24} of EFV with (EFV+MK-8742/EFV) GMR of 0.82 [0.78, 0.86].

Conclusions: MK-8742 concentrations decreased following coadministration with EFV, likely as a result of CYP3A4 induction by EFV. Coadministration of MK-8742 and either RAL or TDF in healthy volunteers did not result in clinically meaningful drug-drug interactions.

Background

- MK-8742, a potent inhibitor of the hepatitis C virus (HCV) NS5A, is being developed as a once-daily treatment for chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-coinfected patients
  - A previous ketoconazole drug-drug interaction study has demonstrated that MK-8742 is a CYP3A4 substrate in vivo
  - MK-8742 is also a substrate of P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro
- Efavirenz (EFV; a non-nucleoside reverse transcriptase inhibitor), raltegravir (RAL; an integrase strand transfer inhibitor), and tenofovir (TDF; a nucleoside reverse transcriptase inhibitor) are recommended first-line therapies for treatment of HIV infection in HIV monoinfected and HIV/HCV-coinfected patients[1]
  - EFV is metabolized by CYP450 3A isoenzymes and is a substrate of CYP2B6[1]
    - It is a mixed inducer and inhibitor, but primarily induces CYP3A and 2B6
  - RAL is primarily eliminated by glucuronidation mediated by the UGT1A1 enzymes[1]
  - TDF does not undergo hepatic metabolism via the CYP enzyme system[1]

Aim

- To evaluate the pharmacokinetic (PK) interactions, safety, and tolerability of MK-8742 when coadministered with TDF, RAL, or EFV in healthy subjects

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    - Period 1: RAL (single dose 400 mg), then washout for ≥3 days
    - Period 2: MK-8742 (single dose 50 mg), then washout for ≥7 days
    - Period 3: RAL (single dose 400 mg) + MK-8742 (single dose 50 mg)
  - Part 3: MK-8742 and EFV administration
    - Period 1: MK-8742 (50 mg once daily) for 8 days, then washout for ≥7 days
    - Period 2: EFV (600 mg once daily) for 14 days
    - Period 3: MK-8742 (50 mg once daily) + EFV (600 mg once daily) for 8 days

Evaluations

- PK parameters
  - Area under the concentration-time curve $(AUC)_{0-24}$, $AUC_{0-\infty}$, maximum concentration (C_{max}), trough concentration (C_{trough}), C_{12}, C_{24}, time to maximum concentration (T_{max}), and apparent terminal half-life ($t_{½}$)
- PK blood sampling scheme
  - MK-8742: predose, and up to 72 hours postdose in part 2 (periods 2 and 3), and up to 24 hours postdose in parts 1 (periods 2 and 3) and 3 (periods 1 and 3)
  - TDF: predose, and up to 24 hours postdose in periods 1 and 3 of part 1
  - RAL: predose, and up to 48 hours postdose in periods 1 and 3 of part 2
  - EFV: predose, and up to 24 hours postdose in periods 2 and 3 in part 3
- Safety: adverse event (AE) monitoring, physical examination, vital signs, electrocardiogram (ECG), and laboratory safety studies

Results

Patient Demographics

- In all 3 parts of the study, most patients were white and non-Hispanic/non-Latino (**Table 1**)

Table 1. Patient Characteristics

	TDF and MK-8742 n = 10	RAL and MK-8742 n = 10	EFV and MK-8742 n = 10
Sex, n			
Male	6	6	5
Female	4	4	5
Race, n			
White	9	7	8
Other	1	3	2
Ethnicity, n			
Hispanic/Latino	1	2	1
Non-Hispanic/non-Latino	9	8	9
Age, y, mean (range)	33 (21, 53)	29 (20, 47)	37 (23, 53)
BMI, kg/m^2, mean (range)	25.18 (19.61, 31.45)	26.28 (20.01, 31.84)	26.45 (21.95, 31.39)

BMI = body mass index; EFV = efavirenz; RAL = raltegravir; TDF = tenofovir.

Pharmacokinetics

MK-8742

- Coadministration of MK-8742 with TDF or RAL did not meaningfully alter the AUC_{0-24} or $AUC_{0-\infty}$ of MK-8742 (**Table 2** and **Figure 1**)
  - There was a 7% and 19% drop in the exposure of MK-8742 when coadministered with TDF and RAL, respectively
- Coadministration of MK-8742 with EFV decreased the AUC_{0-24} of MK-8742 by approximately 54%
  - The MK-8742 AUC_{0-24} geometric least-squares mean ratio (GMR) (90% confidence interval [CI]) for the comparison of MK-8742 + EFV versus MK-8742 alone was 0.46 (0.36, 0.59)
  - The 90% CI was not contained within [0.50, 2.00], the prespecified limits designating lack of a clinically meaningful change; therefore, the primary hypothesis that the AUC_{0-24} of MK-8742 in the presence of EFV is similar to that of MK-8742 alone was not supported

Table 2. Statistical Comparison of Area Under the Plasma Concentration Time Curve of MK-8742 Alone and in Combination With TDF, RAL, or EFV

	Pharmacokinetic Parameter	MK-8742 + Drug/ MK-8742 Alone		Pseudo Within Subject %CV*	MK-8742 Alone			MK-8742 + Drug			
		GMR	90% CI		N	GM	95% CI	Drug	N	GM	95% CI
Part 1 (TDF)	AUC_{0-24}† (μM·h)	0.93	0.82, 1.05	14.657	10	2.45	2.05, 2.94	Tenofovir	10	2.28	1.84, 2.81
Part 2 (RAL)	$AUC_{0-\infty}$† (μM·h)	0.81	0.57, 1.17	43.837	10	2.19	1.69, 2.83	Raltegravir	10	1.78	1.14, 2.77
Part 3 (EFV)	AUC_{0-24}† (μM·h)	0.46	0.36, 0.59	20.528	10	2.21	1.76, 2.77	Efavirenz	7‡	1.01	0.665, 1.54

AE = adverse event; ANOVA = analysis of variance; AUC = area under the concentration-time curve; CI = confidence interval; EFV = efavirenz; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; RAL = raltegravir; TDF = tenofovir.
*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.
‡3 subjects discontinued treatment because of efavirenz-related AEs.

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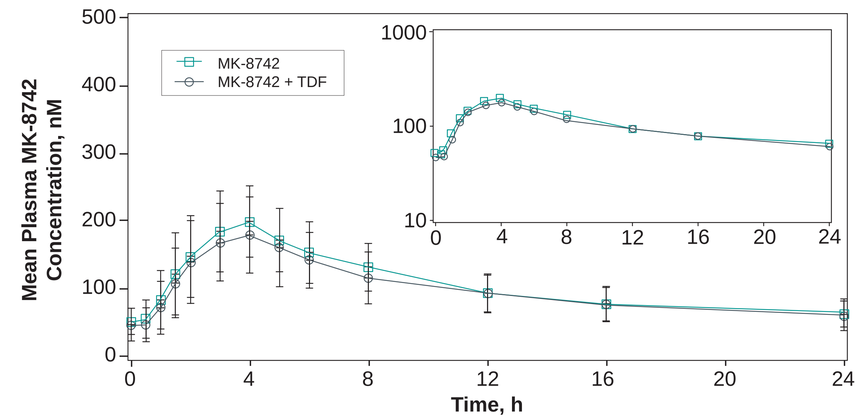
Figure 1. Plasma concentration time profiles for MK-8742 alone and in the presence of (A) tenofovir (TDF), (B) raltegravir (RAL), and (C) efavirenz (EFV).

A



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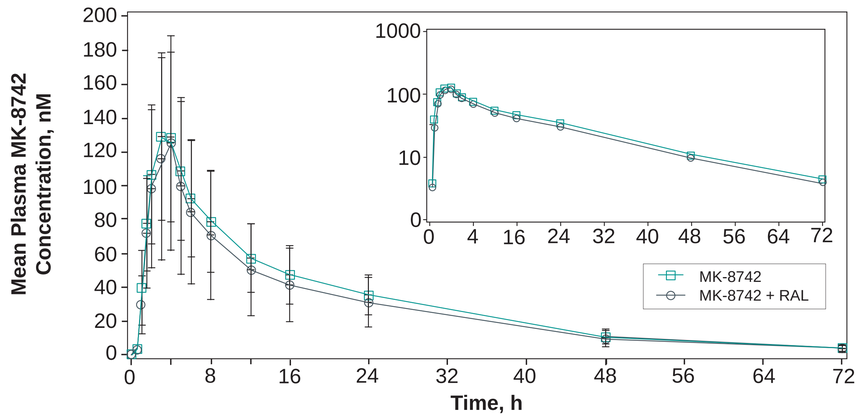

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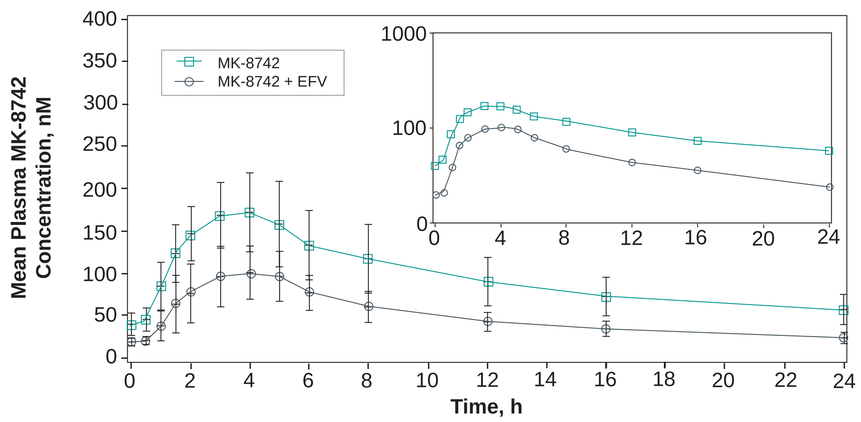


TDF Pharmacokinetics

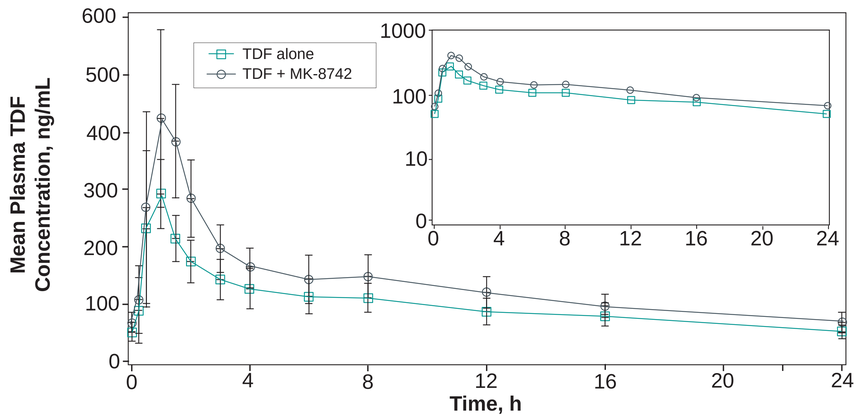
- Coadministration of TDF with MK-8742 increased the plasma $AUC_{0\text{-}24}$ and C_{max} of TDF by approximately 34% and 47%, respectively (**Table 3** and **Figure 2**)

Table 3. Statistical Comparison of Plasma Pharmacokinetics of Tenofovir Alone and in Combination With MK-8742

Pharmacokinetic parameter	TDF Alone			TDF + MK-8742			TDF + MK-8742/TDF Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$† (µg·h/mL)	10	2.36	2.01, 2.77	10	3.17	2.71, 3.71	1.34	1.23, 1.47	10.643
C_{max}† (ng/mL)	10	302	247, 368	10	442	359, 545	1.47	1.32, 1.63	12.879
C_{24}† (ng/mL)	10	51.7	43.0, 62.1	10	66.5	55.3, 79.9	1.29	1.18, 1.41	10.939
T_{max}‡ (h)	10	1.00	0.50, 1.00	10	1.01	0.51, 1.51			

ANOVA = analysis of variance; AUC = area under the concentration-time 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; TDF = tenofovir.
*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}.

Figure 2. Plasma concentration time profiles for tenofovir (TDF) alone and in the presence MK-8742.



RAL Pharmacokinetics

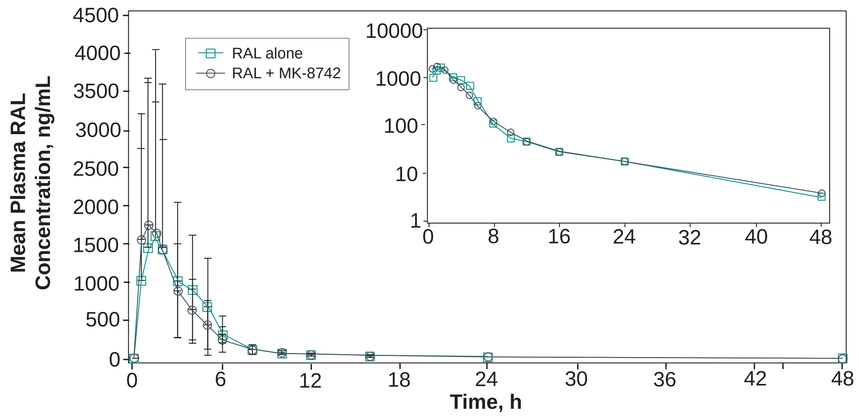
- Coadministration of a single dose of RAL and a single dose of MK-8742 did not meaningfully alter the C_{12} or $AUC_{0\text{-}\infty}$ of RAL (**Table 4** and **Figure 3**)

Table 4. Statistical Comparison of Plasma Pharmacokinetics of Raltegravir Alone and in Combination With MK-8742

Pharmacokinetic Parameter	RAL Alone			RAL + MK-8742			RAL + MK-8742/RAL Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}\infty}$† (µg·h/mL)	10	5.35	3.05, 9.40	10	5.45	3.18, 9.35	1.02	0.81, 1.27	27.207
C_{max}† (ng/mL)	10	1.53	0.806, 2.90	10	1.67	0.839, 3.34	1.09	0.83, 1.44	33.755
C_{12}† (ng/mL)	10	42.7	30.4, 60.1	10	42.4	31.2, 57.5	0.99	0.80, 1.22	25.475
T_{max}‡ (h)	10	2.50	0.50, 5.00	10	1.76	0.51, 5.00			
Apparent terminal $t_{½}$ (h)¶	10	8.56	101.36	10	9.23	53.66			

ANOVA = analysis of variance; AUC = area under the concentration-time curve; C_{max} = maximum concentration; CI = confidence interval; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; RAL = raltegravir; 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, geometric coefficient of variation reported for apparent terminal $t_{½}$.

Figure 3. Plasma concentration time profiles for raltegravir (RAL) alone and in the presence MK-8742.



EFV Pharmacokinetics

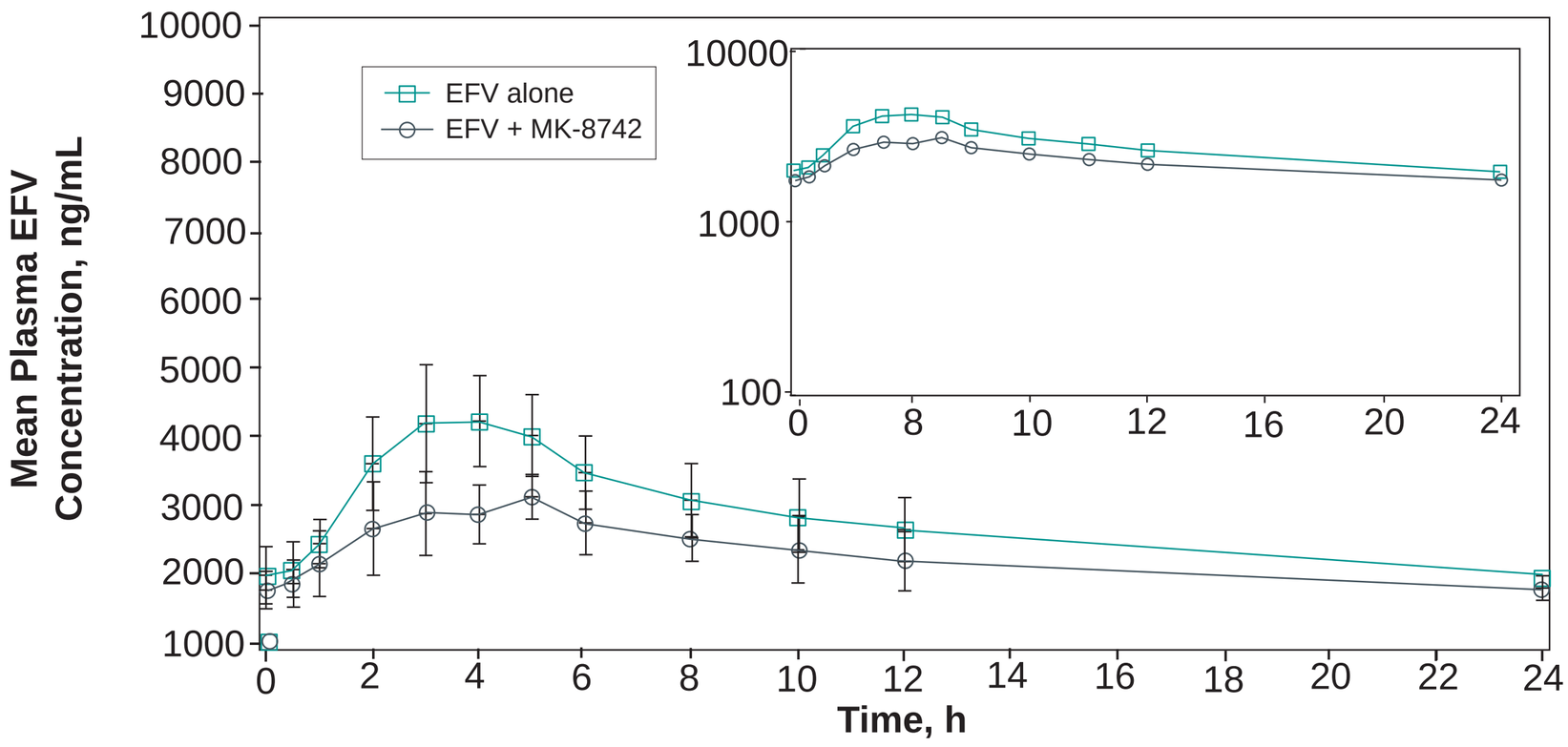
- Concomitant administration of EFV and MK-8742 did not meaningfully alter the plasma $AUC_{0\text{-}24}$ of EFV (**Table 5** and **Figure 4**)
  - The C_{max} for EFV was reduced by 26% in the presence of MK-8742
  - There was an 18% decrease in the $AUC_{0\text{-}24}$ of EFV in the presence of MK-8742; however, the 90% CI (0.78, 0.86) remained within the protocol-specified limits for clinical significance of [0.70, 1.43]

Table 5. Statistical Comparison of Plasma Pharmacokinetics of Efavirenz Alone and in Combination With MK-8742

Pharmacokinetic Parameter	EFV Alone			EFV + MK-8742			EFV + MK-8742 / EFV Alone		Pseudo Within Subject %CV*
	N¶	GM	95% CI	N¶	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$ (µg·h/mL)	7	64.9	56.1, 75.0	7	53.0	46.7, 60.2	0.82	0.78, 0.86	4.465
C_{max}† (µg/mL)	7	4.46	3.85, 5.15	7	3.30	3.04, 3.58	0.74	0.67, 0.82	9.720
C_{24}† (ng/mL)	7	1910	1620, 2250	7	1740	1520, 1990	0.91	0.87, 0.96	4.734
T_{max}‡ (h)	7	3.10	2.00, 5.00	7	4.00	2.00, 5.00			

AE = adverse event; ANOVA = analysis of variance; AUC = area under the concentration-time curve; C_{max} = maximum concentration; CI = confidence interval; EFV = efavirenz; 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}.
¶3 subjects discontinued treatment because of efavirenz-related AEs.

Figure 4. Plasma concentration time profiles for efavirenz (EFV) alone and in the presence MK-8742.



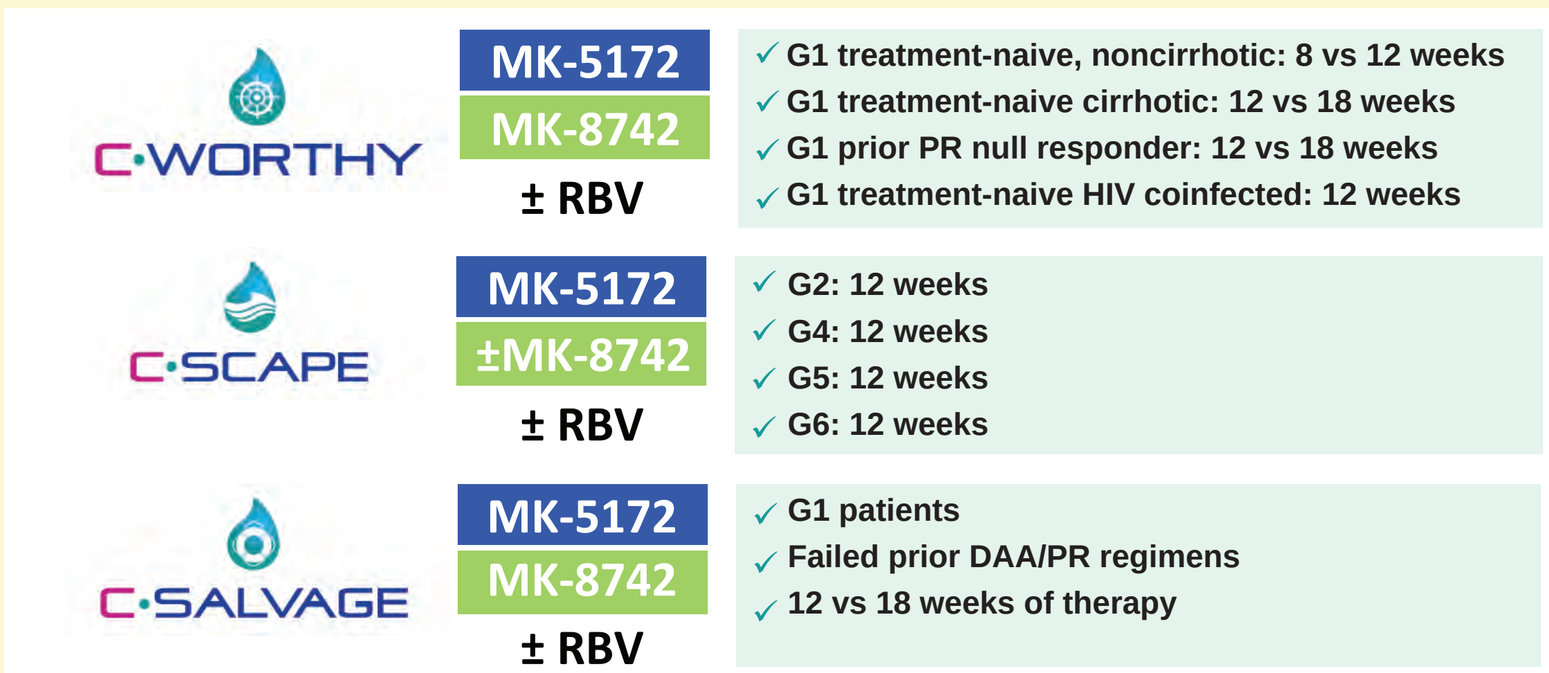
Safety and Tolerability

- No deaths or serious AEs were reported. There were also no consistent treatment-related changes in laboratory values, vital signs, or ECG safety parameters
- TDF and MK-8742
  - All 10 subjects completed the study. Nine subjects reported a total of 28 AEs, 9 of which were considered related to study drugs (MK-8742 alone, n = 8; MK-8742 + TDF, n = 1)
  - All AEs were mild to moderate intensity
  - The most commonly reported AEs were headache (n = 4), diarrhea (n = 3), and abdominal pain (n = 2)
- RAL and MK-8742
  - All 10 subjects completed the study. Two mild AEs were reported
  - One subject reported 2 AEs of fatigue both of which were considered to be related to MK-8742 (MK-8742 alone, n = 1; MK-8742 + RAL, n = 1)
- EFV and MK-8742
  - Three subjects were discontinued because of drug-related AEs following administration of EFV alone (drug eruption, n = 2; drug eruption and generalized maculopapular rash, n = 1).
    - All AEs were mild in intensity, with the exception of a renal colic AE that was severe and this AE was not considered drug related
    - Ten subjects reported a total of 37 clinical AEs, 25 of which were considered to be related to study drugs (EFV, n = 23; MK-8742, n = 2)
    - The most commonly reported AEs were drug eruption, dizziness, and feeling intoxicated (n = 3 each, all in subjects receiving EFV alone)

Summary and Conclusions

- MK-8742 concentrations decreased following coadministration with EFV, possibly as a result of CYP3A4 induction by EFV
- Coadministration of MK-8742 with either RAL or TDF did not result in clinically meaningful drug-drug interactions
  - No dose adjustments would be required by patients with HCV/HIV coinfection undergoing therapy with MK-8742 and TDF or RAL
- Coadministration of MK-8742 with TDF, RAL, or EFV was generally well tolerated
- Ongoing phase 2b studies with MK-8742 (**Figure 5**) will provide additional data regarding the efficacy and safety of this compound in the treatment of HCV infection

Figure 5. Phase 2b studies with MK-8742.



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

Reference

1. 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

SY had a financial relationship within the last 12 months relevant to this presentation with Merck & Co., Inc., Whitehouse Station, NJ. WM, PJ, WY, XH, and JRB are current employees of Merck & Co. Inc., Whitehouse Station, NJ, USA. YZ, JM, and EM were employees of Merck & Co. Inc., Whitehouse Station, NJ, USA at the time this study was conducted. EM is a current employee of Stryker Corporation, Malvern, PA, USA. This study was funded by Merck & Co., Inc., Whitehouse Station, NJ. 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.

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