Ritonavir-Boosted Atazanavir, Lopinavir, & Darunavir Increase HCV NS5A Inhibitor MK-8742 Levels

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Abstract

BACKGROUND: MK-8742, a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS5A, is being developed for the treatment of chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-co-infected patients. MK-8742 is a substrate of CYP3A4, P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro. A ketoconazole DDI study demonstrated that MK-8742 is a CYP3A4 substrate in vivo. Ritonavir (RTV) combinations with atazanavir (ATZr), lopinavir (LPVr), and darunavir (DRVr) are substrates and potent inhibitors of CYP3A4/P-gp in vivo and potentially inhibitors of transporters (e.g., BCRP and OATP). The aim of this study was to assess the potential two-way pharmacokinetic (PK) interaction and tolerability of MK-8742 when coadministered with RTV-boosted HIV protease inhibitors (PI): ATZr, LPVr, and DRVr.

METHODOLOGY: This was an open-label, 3-parallel panel, 3-period study in 10 healthy male and female subjects per panel, ages 19-55 years. In Period 1, subjects received 50 mg of MK-8742 once-daily (QD) for 7 days, followed by a 7 day washout. In Period 2, subjects received either 300 mg ATZ/100 mg RTV QD, 400 LPV/100 mg RTV twice-daily (BID), or 600 mg DRV/100 mg RTV BID for 14 days, immediately followed by Period 3. In Period 3, 50 mg MK-8742 was co-administered with ATZr, LPVr, or DRVr for 7 days.

RESULTS: Coadministration of MK-8742 with ATZr, LPVr, and DRVr was safe and well-tolerated. MK-8742 did not significantly impact ATZ, LPV or DRV PK, with the ATZ $AUC_{0\text{-}24}$ geometric mean ratio (GMR, ATZr+MK-8742/ATZr) [90% confidence interval (CI)] of 1.07 [0.98, 1.17], LPV $AUC_{0\text{-}12}$ GMR (LPVr+MK-8742/ LPVr) [90% CI] of 1.02 [0.92, 1.13], and DRV $AUC_{0\text{-}12}$ GMR (DRV+MK-8742/DRVr) [90% CI] of 0.95 [0.86, 1.06]. MK-8742 exposures were significantly increased when coadministered with the RTV-boosted HIV PIs, with the $AUC_{0\text{-}24}$ GMR (MK-8742+HIV PI-RTV/MK-8742) [90% CI] of 4.76 [4.07, 5.56] with ATZr, 3.71 [3.05, 4.53] with LPVr, and 1.66 [1.35, 2.05] with DRVr.

CONCLUSIONS: Co-administration of MK-8742 with ATZr, LPVr and DRVr did not significantly affect ATZ, LPV and DRV exposures. There was a significant increase in MK-8742 exposures when MK-8742 was co-administered with ATZ, LPV and DRV, which can be attributed to CYP3A4/P-gp inhibition by the HIV PIs/r and potentially inhibition of the transporter (e.g., OATP)-mediated disposition of MK-8742.

Background

- MK-8742, a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS5A, is being developed for the treatment of 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
- Atazanavir (ATZ), lopinavir (LPV), and darunavir (DRV) are substrates and potent inhibitors of CYP3A4/P-gp in vivo and potentially inhibitors of transporters (eg, BCRP and OATP)[1,2]
- Ritonavir (RTV) is a potent inhibitor of CYP3A4 and CYP2D6 and also inhibits several uptake and efflux transporters such as OATP and P-gp[3,4]

Aim

- To assess the potential 2-way pharmacokinetic (PK) interaction and tolerability of MK-8742 when coadministered with RTV-boosted HIV protease inhibitors (PI), such as ATZ/RTV (ATZr), LPV/RTV (LPVr), and DRV/RTV (DRVr)

Patients and Methods

- **Study Design:** An open-label, 3-period, 3-treatment, fixed-sequence, multiple-dose study
- **Subjects:** 10 healthy adult male or female (minimum of 4 female) subjects, 19-55 years old, inclusive
- **Treatments**
  - *Period 1 (7 days):* MK-8742 (50 mg once daily)
  - *Period 2 (14 days):*
    - ATZ (300 mg once daily) + RTV (100 mg once daily) or
    - LPV (400 mg twice daily) + RTV (100 mg twice daily) or
    - DRV (600 mg twice daily) + RTV (100 mg twice daily)
  - *Period 3 (7 days):*
    - MK-8742 (50 mg once daily) + ATZ (300 mg once daily) + RTV (100 mg once daily) or
    - MK-8742 (50 mg once daily) + LPV (400 mg twice daily) + RTV (100 mg twice daily) or
    - MK-8742 (50 mg once daily) + DRV (600 mg twice daily) + RTV (100 mg twice daily)
- **Assessments**
  - *MK-8742 PK:* Plasma PK samples were collected during periods 1 and 3 prior to the morning dose on days 2 to 7, and for 96 hours postdose on day 7
  - *ATZr, LPVr, DRVr PK:*
    - In period 2, plasma PK samples for each of the 3 HIV PIs were collected pre-morning dose on days 4, 7, and 10-14, and then for 24 hours post-morning dose on day 14
    - In period 3, samples were collected prior to the morning dose on days 1-7 and following the morning dose on day 7 for 96 hours (ATZr) or 24 hours (LPVr and DRVr)
  - *Safety:* adverse experiences (AEs), physical examination, vital signs, electrocardiogram (ECG), laboratory safety studies

Results

Patient Demographics

- 6 male and 4 female subjects were enrolled in each part of the study (**Table 1**)
  - Most subjects were white and non-Hispanic/non-Latino

Table 1. Patient Characteristics

	ATZr/MK-8742 n = 10	LPVr/MK-8742 n = 10	DRVr/MK-8742 n = 10
Sex, n			
Male	6	6	6
Female	4	4	4
Race, n			
White	8	9	9
Other	2	1	1
Ethnicity, n			
Hispanic/Latino	2	1	1
Non-Hispanic/non-Latino	8	8	8
Unknown	0	1	1
Age, y, mean (range)	31 (20, 48)	35 (21, 52)	34 (23, 49)
BMI, kg/m^2, mean (range)	24.50 (19.02, 30.51)	25.97 (21.61, 30.46)	26.21 (20.03, 31.88)

ATZr = atazanavir + ritonavir; BMI = body mass index; DRVr = darunavir + ritonavir; LPVr, lopinavir + ritonavir.

ATZ Pharmacokinetics

- ATZ exposures were similar following coadministration of ATZr with MK-8742 compared with ATZr alone (**Table 2**)

Table 2. Steady-State Atazanavir (ATZ) Plasma Pharmacokinetics Following Coadministration of ATZ (300 mg once daily) + Ritonavir (RTV; 100 mg once daily) and MK-8742 (50 mg once daily) vs Administration of ATZ (300 mg once daily) + RTV (100 mg once daily) Alone

Pharmacokinetic Parameter	ATZr Alone			ATZr + MK-8742			ATZr + MK-8742/ ATZr Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$[†] (ng·h/mL)	8	57,800	46,000, 72,500	8	61,700	47,500, 80,000	1.07	0.98, 1.17	9.38
C_{max}[†] (ng/mL)	8	5,740	4,720, 6,970	8	5,840	4,790, 7,110	1.02	0.96, 1.08	6.26
C_{24}[†] (ng/mL)	8	1,230	803, 1,880	8	1,410	899, 2,220	1.15	1.02, 1.29	12.45
T_{max}[‡] (h)	8	3.00	2.00, 5.00	8	3.50	2.00, 5.00			

ANOVA = analysis of variance; ATZr = atazanavir + ritonavir; 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($\sigma A^2 + \sigma B^2 - 2\sigma AB$)/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}.

LPV Pharmacokinetics

- LPV exposures were similar following coadministration of LPVr with MK-8742 compared with LPVr alone (**Table 3**)

Table 3. Steady-State Lopinavir (LPV) Plasma Pharmacokinetics Following Coadministration of LPV (400 mg twice daily) + Ritonavir (RTV; 100 mg twice daily) and MK-8742 (50 mg once daily) vs Administration of LPV (400 mg twice daily) + RTV (100 mg twice daily) Alone

Pharmacokinetic Parameter	LPVr Alone			LPVr + MK-8742			LPVr + MK-8742/LPVr Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$[†] (ng·h/mL)	9	101,000	83,300, 121,000	9	103,000	84,000, 126,000	1.02	0.93, 1.13	11.40
C_{max}[†] (ng/mL)	9	11,600	9,880, 13,600	9	11,800	10,200, 13,800	1.02	0.92, 1.13	11.44
C_{24}[†] (ng/mL)	9	5,780	4,210, 7,930	9	6,170	4,490, 8,480	1.07	0.97, 1.18	10.89
T_{max}[‡] (h)	9	4.00	3.00, 6.00	9	4.01	3.00, 8.00			

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; LPVr = lopinavir + ritonavir; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt($\sigma A^2 + \sigma B^2 - 2\sigma AB$)/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}.

DRV Pharmacokinetics

- DRV exposures were similar following coadministration of DRVr with MK-8742 compared with DRVr alone (**Table 4**)

Table 4. Steady-State Darunavir (DRV) Plasma Pharmacokinetics Following Coadministration of DRV (600 mg twice daily) + Ritonavir (RTV; 100 mg twice daily) and MK-8742 (50 mg once daily) vs Administration of DRV (600 mg twice daily) + RTV (100 mg twice daily) Alone

Pharmacokinetic Parameter	DRV Alone			DRV + MK-8742			DRV + MK-8742/ LPVr Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-}24}$[†] (ng·h/mL)	8	54,000	48,700, 60,000	8	51,400	42,800, 61,900	0.95	0.86, 1.06	10.88
C_{max}[†] (ng/mL)	8	7,190	6,550, 7,900	8	6,800	5,720, 8,090	0.95	0.85, 1.05	10.79
C_{24}[†] (ng/mL)	8	2,870	2,230, 3,700	8	2,700	2,030, 3,600	0.94	0.85, 1.05	11.41
T_{max}[‡] (h)	8	3.00	2.00, 5.00	8	3.50	2.00, 5.00			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; DRVr = darunavir + ritonavir; GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; T_{max} = time to maximum concentration.
*Pseudo within-subject %CV = 100 × Sqrt($\sigma A^2 + \sigma B^2 - 2\sigma AB$)/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}.

MK-8742 Pharmacokinetics

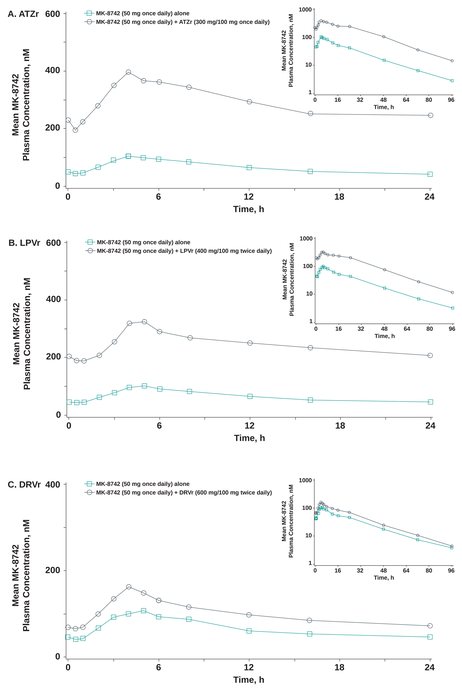
- MK-8742 exposure is markedly increased with coadministration of ritonavir-boosted PI combinations (ATZr, LPVr, DRVr), with MK-8742 $AUC_{0\text{-}24}$ exposures increasing 2- to 5-fold versus MK-8742 administration alone (**Table 5, Figure 1**)

Table 5. Statistical Comparisons of Steady-State MK-8742 Plasma Pharmacokinetics Following Coadministration of MK-8742 (50 mg once daily) and ATZr (300 mg/100 mg once daily), LPVr (400 mg/100 mg twice daily) or DRVr (600 mg/100 mg twice daily) vs Administration of MK-8742 (50 mg once daily) Alone in Healthy Volunteers

	ATZr + MK-8742/MK-8742 Alone GMR (90% CI)	LPVr + MK-8742/MK-8742 Alone GMR (90% CI)	DRVr + MK-8742/MK-8742 Alone GMR (90% CI)
$AUC_{0\text{-}24}$* (μM·h)	4.76 (4.07, 5.56)	3.71 (3.05, 4.53)	1.66 (1.35, 2.05)
C_{max}* (μM)	4.15 (3.46, 4.97)	2.87 (2.29, 3.58)	1.67 (1.36, 2.05)
C_{24}* (nM)	6.45 (5.51, 7.54)	4.58 (3.72, 5.64)	1.82 (1.39, 2.39)

ATZr = atazanavir + ritonavir; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; DRVr = darunavir + ritonavir; GMR = geometric least-squares mean ratio; LPVr = lopinavir + ritonavir.
*Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

Figure 1. MK-8742 steady-state arithmetic mean plasma concentration-time profile following coadministration of MK-8742 (50 mg once daily) with (A) ATZr, (B) LPVr, or (C) DRVr versus administration of MK-8742 (50 mg once daily) alone.



ATZr = atazanavir + ritonavir; DRVr = darunavir + ritonavir; LPVr = lopinavir + ritonavir.

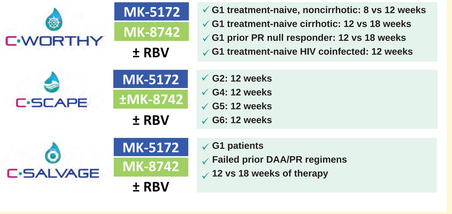
Safety and Tolerability

- MK-8742 alone and in combination with ritonavir-boosted HIV protease inhibitors was generally well tolerated in healthy adult subjects in this study
- There were no deaths, serious AEs, pregnancies, or laboratory AEs reported during the study. There were also no consistent, treatment-related changes in vital signs or ECG
- ATZr ± MK-8742
  - Four subjects reported a total of 13 mild AEs, of which 4 were considered related to study medication (ATZr, n = 3; MK-8742, n = 1)
  - The most commonly reported AEs were headache and rhinorrhea
  - All subjects had elevated bilirubin levels during periods 2 and 3:
  - 8 of 10 subjects completed the study
    - During period 2, 1 subject was discontinued because of an AE of maculopapular rash and 1 subject had an out-of-range bilirubin result protocol violation
- LPVr ± MK-8742
  - Nine subjects reported a total of 69 mild AEs, of which 48 were considered related to study medication (LPVr, n = 47; MK-8742, n = 1)
  - The most commonly reported AEs were diarrhea, abdominal pain, dyspepsia, nausea, and vomiting
  - 9 of 10 subjects completed the study: one subject receiving LPVr withdrew from the study due to multiple gastrointestinal AEs
- DRVr ± MK-8742
  - Seven subjects reported a total of 18 mild AEs, of which 9 were considered related to study medication (DRVr, n = 9)
  - The most commonly reported AE was headache
  - 8 of 10 subjects completed the study: two subjects receiving DRVr were withdrawn due to mild, drug-related papular/macropapular rashes

Conclusions

- Coadministration of MK-8742 with ATZr, LPVr, and DRVr did not significantly affect atazanavir, lopinavir, or darunavir exposures
- There was a significant increase in MK-8742 exposures when MK-8742 was coadministered with ATZr, LPVr, and DRVr, which can be attributed to CYP3A4/P-gp inhibition by the HIV PIs/r and potentially inhibition of the transporter (eg, OATP)-mediated disposition of MK-8742
- Ongoing phase 2b studies with MK-8742 (**Figure 2**) will provide additional data regarding the efficacy and safety of this compound in the treatment of HCV infection

Figure 2 Phase 2b studies with MK-8742.



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

References

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3. Josephson F. *J Intern Med.* 2010;268(6):530-539.
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Disclosures

SY had a financial relationship within the last 12 months relevant to this presentation with Merck & Co., Inc., Whitehouse Station, NJ. WWY, WM, PJ, XH, and JRB are current employees of Merck & Co. Inc., Whitehouse Station, NJ, USA. JM and EM were employees were 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.

This study was funded by Merck, Whitehouse Station, NJ, USA

Abstract

BACKGROUND: MK-8742, a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS5A, is being developed for the treatment of chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-co-infected patients. MK-8742 is a substrate of CYP3A4, P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro. A ketoconazole DDI study demonstrated that MK-8742 is a CYP3A4 substrate in vivo. Ritonavir (RTV) combinations with atazanavir (ATZr), lopinavir (LPVr), and darunavir (DRVr) are substrates and potent inhibitors of CYP3A4/P-gp in vivo and potentially inhibitors of transporters (e.g., BCRP and OATP). The aim of this study was to assess the potential two-way pharmacokinetic (PK) interaction and tolerability of MK-8742 when coadministered with RTV-boosted HIV protease inhibitors (PI): ATZr, LPVr, and DRVr.

METHODOLOGY: This was an open-label, 3-parallel panel, 3-period study in 10 healthy male and female subjects per panel, ages 19-55 years. In Period 1, subjects received 50 mg of MK-8742 once-daily (QD) for 7 days, followed by a 7 day washout. In Period 2, subjects received either 300 mg ATZ/100 mg RTV QD, 400 LPV/100 mg RTV twice-daily (BID), or 600 mg DRV/100 mg RTV BID for 14 days, immediately followed by Period 3. In Period 3, 50 mg MK-8742 was co-administered with ATZr, LPVr, or DRVr for 7 days.

RESULTS: Coadministration of MK-8742 with ATZr, LPVr, and DRVr was safe and well-tolerated. MK-8742 did not significantly impact ATZ, LPV or DRV PK, with the ATZ AUC_{0-24} geometric mean ratio (GMR, ATZr+MK-8742/ ATZr) [90% confidence interval (CI)] of 1.07 [0.98, 1.17], LPV AUC_{0-12} GMR (LPVr+MK-8742/ LPVr) [90% CI] of 1.02 [0.92, 1.13], and DRV AUC_{0-12} GMR (DRVr+MK-8742/DRVr) [90% CI] of 0.95 [0.86, 1.06]. MK-8742 exposures were significantly increased when coadministered with the RTV-boosted HIV PIs, with the AUC_{0-24} GMR (MK-8742+HIV PI-RTV/MK-8742) [90% CI] of 4.76 [4.07, 5.56] with ATZr, 3.71 [3.05, 4.53] with LPVr, and 1.66 [1.35, 2.05] with DRVr.

CONCLUSIONS: Co-administration of MK-8742 with ATZr, LPVr and DRVr did not significantly affect ATZ, LPV and DRV exposures. There was a significant increase in MK-8742 exposures when MK-8742 was co-administered with ATZ, LPV and DRV, which can be attributed to CYP3A4/P-gp inhibition by the HIV PIs/r and potentially inhibition of the transporter (e.g., OATP)-mediated disposition of MK-8742.

Background

- MK-8742, a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS5A, is being developed for the treatment of 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
- Atazanavir (ATZ), lopinavir (LPV), and darunavir (DRV) are substrates and potent inhibitors of CYP3A4/P-gp in vivo and potentially inhibitors of transporters (eg, BCRP and OATP)[1,2]
- Ritonavir (RTV) is a potent inhibitor of CYP3A4 and CYP2D6 and also inhibits several uptake and efflux transporters such as OATP and P-gp[3,4]

Aim

- To assess the potential 2-way pharmacokinetic (PK) interaction and tolerability of MK-8742 when coadministered with RTV-boosted HIV protease inhibitors (PI), such as ATZ/RTV (ATZr), LPV/RTV (LPVr), and DRV/RTV (DRVr)

Patients and Methods

- **Study Design:** An open-label, 3-period, 3-treatment, fixed-sequence, multiple-dose study
- **Subjects:** 10 healthy adult male or female (minimum of 4 female) subjects, 19-55 years old, inclusive
- **Treatments**
  - *Period 1 (7 days):* MK-8742 (50 mg once daily)
  - *Period 2 (14 days):*
    - ATZ (300 mg once daily) + RTV (100 mg once daily) or
    - LPV (400 mg twice daily) + RTV (100 mg twice daily) or
    - DRV (600 mg twice daily) + RTV (100 mg twice daily)
  - *Period 3 (7 days):*
    - MK-8742 (50 mg once daily) + ATZ (300 mg once daily) + RTV (100 mg once daily) or
    - MK-8742 (50 mg once daily) + LPV (400 mg twice daily) + RTV (100 mg twice daily) or
    - MK-8742 (50 mg once daily) + DRV (600 mg twice daily) + RTV (100 mg twice daily)
- **Assessments**
  - *MK-8742 PK:* Plasma PK samples were collected during periods 1 and 3 prior to the morning dose on days 2 to 7, and for 96 hours postdose on day 7
  - *ATZr, LPVr, DRVr PK:*
    - In period 2, plasma PK samples for each of the 3 HIV PIs were collected pre-morning dose on days 4, 7, and 10-14, and then for 24 hours post-morning dose on day 14
    - In period 3, samples were collected prior to the morning dose on days 1-7 and following the morning dose on day 7 for 96 hours (ATZr) or 24 hours (LPVr and DRVr)
  - *Safety:* adverse experiences (AEs), physical examination, vital signs, electrocardiogram (ECG), laboratory safety studies

Results

Patient Demographics

- 6 male and 4 female subjects were enrolled in each part of the study (**Table 1**)
  - Most subjects were white and non-Hispanic/non-Latino

Table 1. Patient Characteristics

	ATZr/MK-8742 n = 10	LPVr/MK-8742 n = 10	DRVr/MK-8742 n = 10
Sex, n			
Male	6	6	6
Female	4	4	4
Race, n			
White	8	9	9
Other	2	1	1
Ethnicity, n			
Hispanic/Latino	2	1	1
Non-Hispanic/non-Latino	8	8	8
Unknown	0	1	1
Age, y, mean (range)	31 (20, 48)	35 (21, 52)	34 (23, 49)
BMI, kg/m^2, mean (range)	24.50 (19.02, 30.51)	25.97 (21.61, 30.46)	26.21 (20.03, 31.88)

ATZr = atazanavir + ritonavir; BMI = body mass index; DRVr = darunavir + ritonavir; LPVr, lopinavir + ritonavir.

ATZ Pharmacokinetics

- ATZ exposures were similar following coadministration of ATZr with MK-8742 compared with ATZr alone (**Table 2**)

Table 2. Steady-State Atazanavir (ATZ) Plasma Pharmacokinetics Following Coadministration of ATZ (300 mg once daily) + Ritonavir (RTV; 100 mg once daily) and MK-8742 (50 mg once daily) vs Administration of ATZ (300 mg once daily) + RTV (100 mg once daily) Alone

	ATZr Alone			ATZr + MK-8742			ATZr + MK-8742/ ATZr Alone		Pseudo Within Subject %CV*
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}† (ng·h/mL)	8	57,800	46,000, 72,500	8	61,700	47,500, 80,000	1.07	0.98, 1.17	9.38
C_{max}† (ng/mL)	8	5,740	4,720, 6,970	8	5,840	4,790, 7,110	1.02	0.96, 1.08	6.26
C_{24}† (ng/mL)	8	1,230	803, 1,880	8	1,410	899, 2,220	1.15	1.02, 1.29	12.45
T_{max}‡ (h)	8	3.00	2.00, 5.00	8	3.50	2.00, 5.00			

ANOVA = analysis of variance; ATZr = atazanavir + ritonavir; 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}.

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LPV Pharmacokinetics

- LPV exposures were similar following coadministration of LPVr with MK-8742 compared with LPVr alone (**Table 3**)

Table 3. Steady-State Lopinavir (LPV) Plasma Pharmacokinetics Following Coadministration of LPV (400 mg twice daily) + Ritonavir (RTV; 100 mg twice daily) and MK-8742 (50 mg once daily) vs Administration of LPV (400 mg twice daily) + RTV (100 mg twice daily) Alone

Pharmacokinetic Parameter	LPVr Alone			LPVr + MK-8742			LPVr + MK-8742/LPVr Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}† (ng·h/mL)	9	101,000	83,300, 121,000	9	103,000	84,000, 126,000	1.02	0.93, 1.13	11.40
C_{max}† (ng/mL)	9	11,600	9,880, 13,600	9	11,800	10,200, 13,800	1.02	0.92, 1.13	11.44
C_{24}† (ng/mL)	9	5,780	4,210, 7,930	9	6,170	4,490, 8,480	1.07	0.97, 1.18	10.89
T_{max}‡ (h)	9	4.00	3.00, 6.00	9	4.01	3.00, 8.00			

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; LPVr = lopinavir + ritonavir; 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}.

DRV Pharmacokinetics

- DRV exposures were similar following coadministration of DRVr with MK-8742 compared with DRVr alone (**Table 4**)

Table 4. Steady-State Darunavir (DRV) Plasma Pharmacokinetics Following Coadministration of DRV (600 mg twice daily) + Ritonavir (RTV; 100 mg twice daily) and MK-8742 (50 mg once daily) vs Administration of DRV (600 mg twice daily) + RTV (100 mg twice daily) Alone

Pharmacokinetic Parameter	DRVr Alone			DRVr + MK-8742			DRVr + MK-8742/ LPVr Alone		Pseudo Within Subject %CV*
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}† (ng·h/mL)	8	54,000	48,700, 60,000	8	51,400	42,800, 61,900	0.95	0.86, 1.06	10.88
C_{max}† (ng/mL)	8	7,190	6,550, 7,900	8	6,800	5,720, 8,090	0.95	0.85, 1.05	10.79
C_{24}† (ng/mL)	8	2,870	2,230, 3,700	8	2,700	2,030, 3,600	0.94	0.85, 1.05	11.41
T_{max}‡ (h)	8	3.00	2.00, 5.00	8	3.50	2.00. 5.00			

ANOVA = analysis of variance; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; DRVr = darunavir + ritonavir; 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}.

MK-8742 Pharmacokinetics

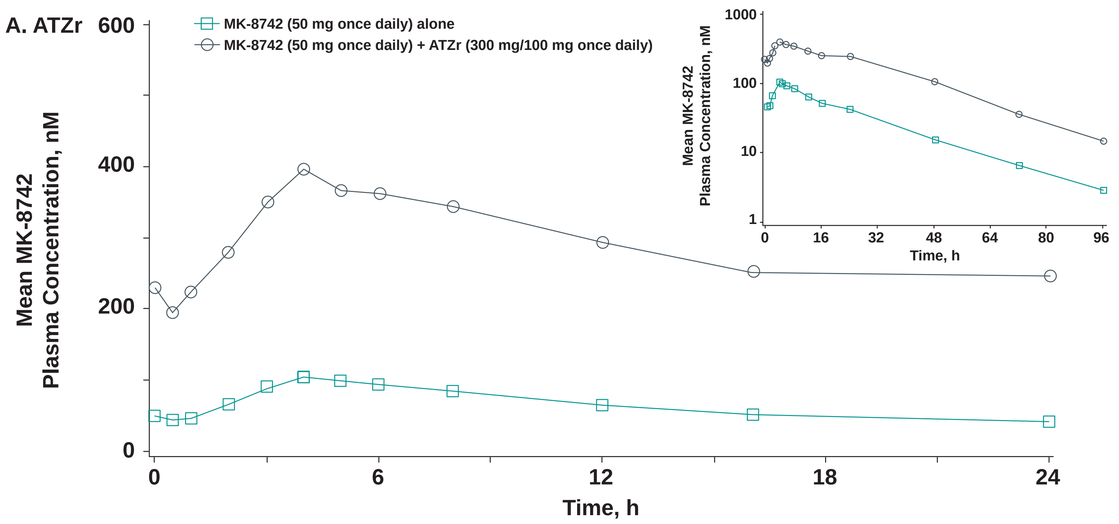
- MK-8742 exposure is markedly increased with coadministration of ritonavir-boosted PI combinations (ATZr, LPVr, DRVr), with MK-8742 AUC_{0-24} exposures increasing 2- to 5-fold versus MK-8742 administration alone **(Table 5, Figure 1)**

Table 5. Statistical Comparisons of Steady-State MK-8742 Plasma Pharmacokinetics Following Coadministration of MK-8742 (50 mg once daily) and ATZr (300 mg/100 mg once daily), LPVr (400 mg/100 mg twice daily) or DRVr (600 mg/100 mg twice daily) vs Administration of MK-8742 (50 mg once daily) Alone in Healthy Volunteers

	ATZr + MK-8742/MK-8742 Alone GMR (90% CI)	LPVr + MK-8742/MK-8742 Alone GMR (90% CI)	DRVr + MK-8742/MK-8742 Alone GMR (90% CI)
AUC_{0-24}* (µM·h)	4.76 (4.07, 5.56)	3.71 (3.05, 4.53)	1.66 (1.35, 2.05)
C_{max}* (µM)	4.15 (3.46, 4.97)	2.87 (2.29, 3.58)	1.67 (1.36, 2.05)
C_{24}* (nM)	6.45 (5.51, 7.54)	4.58 (3.72, 5.64)	1.82 (1.39, 2.39)

ATZr = atazanavir + ritonavir; AUC = area under the time-concentration curve; C_{max} = maximum concentration; CI = confidence interval; DRVr = darunavir + ritonavir; GMR = geometric least-squares mean ratio; LPVr = lopinavir + ritonavir.
*Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

Figure 1. MK-8742 steady-state arithmetic mean plasma concentration-time profile following coadministration of MK-8742 (50 mg once daily) with (A) ATZr, (B) LPVr, or (C) DRVr versus administration of MK-8742 (50 mg once daily) alone.



ATZr = atazanavir + ritonavir; DRVr = darunavir + ritonavir; LPVr = lopinavir + ritonavir.

Safety and Tolerability

- MK-8742 alone and in combination with ritonavir-boosted HIV protease inhibitors was generally well tolerated in healthy adult subjects in this study
- There were no deaths, serious AEs, pregnancies, or laboratory AEs reported during the study. There were also no consistent, treatment-related changes in vital signs or ECG
- ATZr ± MK-8742
  - Four subjects reported a total of 13 mild AEs, of which 4 were considered related to study medication (ATZr, n = 3; MK-8742, n = 1)
  - The most commonly reported AEs were headache and rhinorrhea
  - All subjects had elevated bilirubin levels during periods 2 and 3:
  - 8 of 10 subjects completed the study
    - During period 2, 1 subject was discontinued because of an AE of maculopapular rash and 1 subject had an out-of-range bilirubin result protocol violation
- LPVr ± MK-8742
  - Nine subjects reported a total of 69 mild AEs, of which 48 were considered related to study medication (LPVr, n = 47; MK-8742, n = 1)
  - The most commonly reported AEs were diarrhea, abdominal pain, dyspepsia, nausea, and vomiting
  - 9 of 10 subjects completed the study: one subject receiving LPVr withdrew from the study due to multiple gastrointestinal AEs
- DRVr ± MK-8742
  - Seven subjects reported a total of 18 mild AEs, of which 9 were considered related to study medication (DRVr, n = 9)
  - The most commonly reported AE was headache
  - 8 of 10 subjects completed the study: two subjects receiving DRVr were withdrawn due to mild, drug-related papular/macropapular rashes

Conclusions

- Coadministration of MK-8742 with ATZr, LPVr, and DRVr did not significantly affect atazanavir, lopinavir, or darunavir exposures
- There was a significant increase in MK-8742 exposures when MK-8742 was coadministered with ATZr, LPVr, and DRVr, which can be attributed to CYP3A4/P-gp inhibition by the HIV PIs/r and potentially inhibition of the transporter (eg, OATP)-mediated disposition of MK-8742
- Ongoing phase 2b studies with MK-8742 **(Figure 2)** will provide additional data regarding the efficacy and safety of this compound in the treatment of HCV infection

Figure 2 Phase 2b studies with MK-8742.

C-WORTHY	MK-5172 + MK-8742 ± RBV	✓ G1 treatment-naive, noncirrhotic: 8 vs 12 weeks ✓ G1 treatment-naive cirrhotic: 12 vs 18 weeks ✓ G1 prior PR null responder: 12 vs 18 weeks ✓ G1 treatment-naive HIV coinfected: 12 weeks
C-SCAPE	MK-5172 + ±MK-8742 ± RBV	✓ G2: 12 weeks ✓ G4: 12 weeks ✓ G5: 12 weeks ✓ G6: 12 weeks
C-SALVAGE	MK-5172 + MK-8742 ± RBV	✓ G1 patients ✓ Failed prior DAA/PR regimens ✓ 12 vs 18 weeks of therapy

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

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Disclosures

SY had a financial relationship within the last 12 months relevant to this presentation with Merck & Co., Inc., Whitehouse Station, NJ. WWY, WM, PJ, XH, and JRB are current employees of Merck & Co. Inc., Whitehouse Station, NJ, USA. JM and EM were employees were 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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