Age and Gender Effects on the Pharmacokinetics of HCV NS5A Inhibitor MK-8742

WL Marshall[1], WW Yeh[1], D Stypinski[2], P Auger[2], L Caro[1], P Jumes[1], X Huang[1], DP Dreyer[1], H-P Feng[1], T O'Reilly[2], B DeGroot[2], T Ward[2], and JR Butterton[1]

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

Abstract

Background: MK-8742 is a potent, once-daily, inhibitor of the hepatitis C virus (HCV) nonstructural protein NS5A being developed for the treatment of chronic HCV infection. This study was the first comparison of MK-8742 pharmacokinetics (PK) between males and females, as well as the first comparison between healthy young males and healthy elderly subjects.

Methodology: This was a double-blind, placebo-controlled, randomized, single-dose study designed to evaluate the safety, tolerability, and PK of MK-8742 in healthy elderly male and female subjects. Panel A and Panel B consisted of 14 healthy elderly male (age 65-78 years) and 14 healthy elderly female (age 65-80 years) subjects, respectively. Twelve (12) subjects per panel were randomized to receive a single oral dose of 100 mg MK-8742, and 2 subjects per panel received matching placebo. Panel C consisted of 8 young (age 22-45 years) male subjects; 6 received MK-8742 and 2 received placebo.

Results: A single dose of 100 mg MK-8742 was well tolerated in the healthy elderly males and females and healthy young males in this study. The MK-8742 $AUC_{0-\infty}$, C_{max}, and C_{24h} geometric mean ratios (GMRs) (90% confidence intervals [90% CIs]) for the comparison of a single dose of 100 mg MK-8742 administered to healthy elderly females vs healthy elderly male subjects were 1.67 (1.12, 2.48), 1.75 (1.16, 2.66) and 1.58 (1.07, 2.33), respectively. Additional exploratory analyses were conducted to adjust for body weight or BMI. The resulting $AUC_{0-\infty}$ GMRs (90% CIs) for the comparison of a single dose of 100 mg MK-8742 administered to healthy elderly female vs healthy elderly male subjects were 1.33 (0.83, 2.14), when adjusted for body weight, and 1.64 (1.10, 2.45), when adjusted for BMI. Similar results were obtained for the C_{max} and C_{24h} parameters following these additional analyses. The MK-8742 $AUC_{0-\infty}$, C_{max}, and C_{24h} GMRs (90% CIs) for the comparison of a single dose of 100 mg MK-8742 administered to healthy elderly males vs healthy young males were 1.02 (0.69, 1.53), 0.91 (0.60, 1.38), and 0.97 (0.66, 1.44).

Conclusions: The plasma exposures following a single 100 mg dose of MK-8742 in healthy elderly female subjects is approximately 70% greater than that observed in healthy elderly male subjects. The plasma $AUC_{0-\infty}$ is approximately 33% greater in healthy elderly female subjects when adjusted for weight, suggesting that the observed gender effect may partially be explained by gender differences in body weight. A single 100 mg administration of MK-8742 results in similar exposures in healthy elderly male and healthy young male subjects. MK-8742 was well tolerated in the healthy elderly male and female subjects in this study.

Background

- MK-8742 is a potent, once-daily inhibitor of the hepatitis C virus (HCV) nonstructural protein NS5A being developed for the treatment of chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-coinfected patients.
- This study represented the first comparison of MK-8742 PK between healthy elderly males and females, providing preliminary safety data for this study population age group in HCV-infected patients, as well as the first comparison between healthy young males and healthy elderly subjects.
- MK-8742, a hepatitis C virus (HCV) NS5A inhibitor with potent activity against several HCV genotypes, is being developed as a potential component of an all-oral, direct-acting antiviral regimen. It is currently in Phase 3 development for use in in combination with MK-5172, an HCV NS3/4A protease inhibitor, for the treatment of chronic HCV infection.

Aims

- To evaluate safety and tolerability of a single oral dose of MK-8742 in healthy elderly male, healthy elderly female, and healthy young male subjects.
- To obtain preliminary plasma PK data (eg, $AUC_{0-\infty}$, C_{24}, C_{max}, t_{max}, apparent terminal $t_{½}$) after administration of single oral doses of MK-8742 to healthy elderly male subjects compared to healthy elderly female subjects and compared to healthy young male subjects (including historical control data from 6 healthy young male subjects from MK-8742 PN001-Part I).

Subjects and Methods

- **Study Design:** Double-blind, randomized, placebo-controlled, single-dose study.
- **Subjects:** 36 healthy, nonsmoking elderly males and females between 65 and 80 years of age and nonsmoking young male subjects between 18 and 50 years of age, with a body mass index (BMI) of ≤32 kg/m^2.
- **Treatments:**
  - **Panel A:** 14 healthy elderly male subjects [n = 12 active (100 mg MK-8742) and n = 2 placebo].
  - **Panel B:** 14 healthy elderly female subjects [n = 12 active (100 mg MK-8742) and n = 2 placebo].
  - **Panel C:** 8 healthy young male subjects [n = 6 active (100 mg MK-8742) and n = 2 placebo].
  - **Historical Data:** 6 healthy male subjects (age 22-45, BMI ≤30.14 kg/m^2) from MK-8742 PN001-Part I, 100 mg dose.
- **Assessments**
- **Safety:** adverse experiences (AEs), physical examination, vital signs, electrocardiograms (ECGs), laboratory safety studies.
- **MK-8742 PK:** Plasma PK samples were collected from subjects in each Panel at predose and at specified time points over 120 hours following the MK-8742 dose in each treatment period.
- Exposure parameters ($AUC_{0-\infty}$, AUC_{0-24}, C_{max}, C_{24}) were log transformed (on natural log-scale) and analyzed in an analysis of variance (ANOVA) model with a fixed effect for population (elderly male, elderly female, and young male). For each comparison of interest, least-squares (LS) means and corresponding 95% confidence intervals (CIs) and differences between LS means and corresponding 90% CIs were generated from the ANOVA model. The backtransformed inferential results [geometric mean (GM) and their 95% CIs and GMRs and their 90% CIs] were reported. Separate exploratory analyses were performed with BMI and total body weight (TBW) as covariates in the model.

Results

Subject Demographics

- Of the 36 subjects enrolled, 26 were White and non-Hispanic/non-Latino, 8 were Hispanic or Latino, and 2 were Black or African American (**Table 1**).

Table 1. Subject Characteristics

		Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Overall N = 36	Range	22 - 80	150.0 - 190.0	50.5 - 99.6	20.33 - 31.76
	Mean	62	169.4	78.1	27.09
Elderly Female N = 14	Range	65 - 80	150.0 - 170.0	50.5 - 84.3	21.50 - 31.69
	Mean	71	159.4	67.9	26.56
Elderly Male N = 14	Range	65 - 78	161.0 - 187.0	65.7 - 99.6	22.68 - 31.76
	Mean	70	174.5	83.5	27.39
Young Male N = 8	Range	22 - 45	170.0 - 190.0	73.6 - 99.6	20.33 - 31.67
	Mean	34	177.8	86.5	27.49

BMI = body mass index.

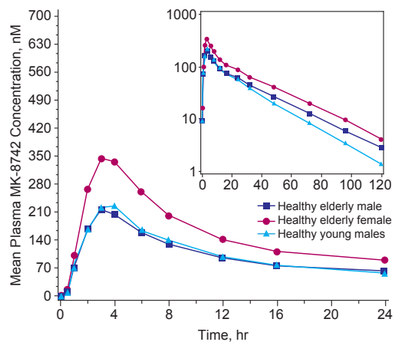
Safety and Tolerability

- A single dose of 100 mg MK-8742 was well tolerated in the healthy elderly males and females and healthy young males in this study.
- There were no deaths, serious AEs, or laboratory AEs reported during the study. There were also no consistent, treatment-related changes in the safety laboratory profiles, vital signs, or ECG assessments during the study.
- A total of 8 subjects reported a total of 9 treatment-emergent adverse experiences; 4 of which were considered treatment-related: constipation, abdominal distension, and myalgia following MK-8742; and eczema following placebo.

MK-8742 Pharmacokinetics

- Administration of MK-8742 resulted in higher MK-8742 exposure (by approximately 70%) in elderly female subjects as compared with elderly male subjects (**Figure 1, Table 2**).
  - Similar results were observed for MK-8742 peak exposure (C_{max}) and trough concentrations (C_{24}), indicating a gender effect in the elderly.
    - Absence of differences in the mean apparent terminal $t_{½}$ observed between elderly males and females indicates possible differences in absorption and/or distribution parameters.
- PK parameters were similar between elderly male and young male groups, suggesting no effect on MK-8742 exposure due to age (**Figure 1, Table 3**) (pooling of the data from the elderly male and elderly female subjects was not allowed by the statistical plan because of the differences in the pharmacokinetic parameters between elderly males and elderly females [the 70% higher $AUC_{0-\infty}$ in females compared to males]).

Figure 1. Arithmetic Mean Plasma Concentration-Time Profiles of MK-8742 Following the Administration of a Single Dose of 100 mg MK-8742 to Healthy Elderly Male (n = 12), Healthy Elderly Female (n = 12), and Healthy Young Male (n = 6) Subjects



Inset = semi-log scale; LOQ = 0.283nM.

Table 2. Statistical Comparison Summary of Plasma Pharmacokinetics of MK-8742 Following the Administration of a Single Dose of 100 mg MK-8742 to Healthy Elderly Male and to Healthy Elderly Female Subjects

Pharmacokinetic Parameter	Elderly Females			Elderly Males			Elderly Females/ Elderly Males		rMSE‡
	n	GM	95% CI	n	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$† (µM•hr)	12	6.00	(4.28, 8.42)	12	3.60	(2.57, 5.05)	1.67	(1.12, 2.48)	0.577
C_{max}† (nM)	12	316	(221, 450)	12	180	(126, 257)	1.75	(1.16, 2.66)	0.604
C_{24}† (nM)	12	81.2	(58.3, 113)	12	51.4	(36.9, 71.6)	1.58	(1.07, 2.33)	0.564
t_{max}§ (hr)	12	3.50	(2.99, 4.00)	12	3.02	(2.00, 4.01)			
Apparent terminal $t_{½}$‖ (hr)	12	22.05	9.95	12	21.20	20.84			

Single oral dose of 100 mg (10 x 10 mg capsules) MK-8742 administered to healthy elderly males and females. †Back-transformed least-squares mean and confidence interval from ANOVA model performed on natural logtransformed values; ‡rMSE: Square root of the residual variance component from the ANOVA model. rMSE*100% approximates the study %CV on the raw scale; §Median (min, max) reported for t_{max}; ‖Geometric mean and geometric CV are reported for apparent terminal $t_{½}$. GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; CI = confidence interval.

Table 3. Statistical Comparison Summary of Plasma Pharmacokinetics of MK-8742 Following the Administration of a Single Dose of 100 mg MK-8742 to Healthy Elderly Male and to Healthy Young Male Subjects (Panel C and Historical Control Data)

Pharmacokinetic Parameter	Elderly Males			Young Males			Elderly Males/ Young Males		rMSE‡
	n	GM	95% CI	n	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$† (µM•hr)	12	3.60	(2.57, 5.05)	12	3.51	(2.50, 4.93)	1.02	(0.69, 1.53)	0.577
C_{max}† (nM)	12	180	(126, 257)	12	199	(139, 283)	0.91	(0.60, 1.38)	0.604
C_{24}† (nM)	12	51.4	(36.9, 71.6)	12	52.8	(37.9, 73.5)	0.97	(0.66, 1.44)	0.564
t_{max}§ (hr)	12	3.02	(2.00, 4.01)	12	3.50	(3.00, 4.00)			
Apparent terminal $t_{½}$‖ (hr)	12	21.20	20.84	12	18.58	15.95			

Single oral dose of 100 mg (10 x 10 mg capsules) MK-8742 administered to healthy elderly males and young males. †Back-transformed least-squares mean and confidence interval from ANOVA model performed on natural logtransformed values; ‡rMSE: Square root of the residual variance component from the ANOVA model. rMSE*100% approximates the study %CV on the raw scale; §Median (min, max) are reported for t_{max}; ‖Geometric mean and geometric CV are reported for apparent terminal $t_{½}$, ¶Parameter AUC_{0-24} was not included in the historical data. GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; CI = confidence interval.

Exploratory Analyses of BMI and Total Body Weight

- MK-8742 total exposure ($AUC_{0-\infty}$) with BMI as a covariate was similar to that without the BMI covariate in the model (**Table 4**).
- MK-8742 total exposure ($AUC_{0-\infty}$) with total body weight as a covariate was approximately 33% greater in healthy elderly female subjects as compared with healthy elderly males (**Table 5**).
  - The weight effect was apparent in elderly females due to lower exposures in 4 women weighing >80 kg (relative to the other 8 elderly women who received the active treatment) (**Figure 2**).
  - The weight effect was not apparent among elderly female subjects who weighed less than 70 kg.
  - No effect of increased weight on decreased MK-8742 exposures was apparent in male subjects.
- Similar results were observed for C_{max}, AUC_{0-24}, and C_{24}.
- Overall, the results suggested that the observed gender effect may partially be explained by the difference in body weight between sexes.

Table 4. Statistical Comparison Summary of Plasma Pharmacokinetics of MK-8742 With BMI as Covariate Following the Administration of a Single Dose of 100 mg MK-8742 to Healthy Elderly Male and to Healthy Elderly Female Subjects

Pharmacokinetic Parameter	Healthy Elderly Female Subjects			Healthy Elderly Male Subjects			(Healthy Elderly Female Subjects/ Healthy Elderly Male Subjects)		rMSE‡
	n	GM	95% CI	n	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$† (µM•hr)	12	5.95	(4.23, 8.37)	12	3.63	(2.58, 5.10)	1.64	(1.10, 2.45)	0.574
C_{max}† (nM)	12	312	(219, 445)	12	182	(128, 259)	1.72	(1.13, 2.60)	0.597
C_{24}† (nM)	12	80.7	(57.6, 113)	12	51.7	(37.0, 72.4)	1.56	(1.05, 2.31)	0.566
t_{max}‖ (hr)	12	3.50	(2.99, 4.00)	12	3.02	(2.00, 4.01)			
Apparent terminal $t_{½}$§ (hr)	12	22.05	9.95	12	21.20	20.84			

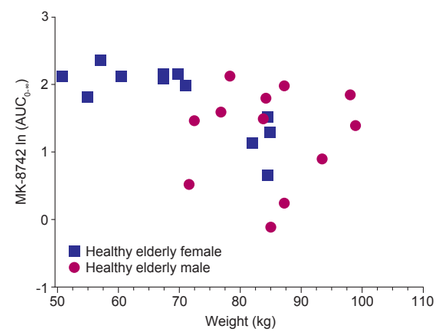
Single oral dose of 100 mg (10 x 10 mg capsules) MK-8742 administered to healthy elderly males and females. †Back-transformed least-squares mean and confidence interval from ANOVA model containing fixed effect for population and continuous covariate for BMI (P>0.05), and performed on natural log-transformed values; ‡rMSE: Square root of the residual variance component from the ANOVA model. rMSE*100% approximates the study %CV on the raw scale; ‖Median (min, max) reported for t_{max}; §Geometric mean and geometric CV are reported for apparent terminal $t_{½}$. GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; CI = confidence interval.

Table 5. Statistical Comparison Summary of Plasma Pharmacokinetics of MK-8742 With Weight as Covariate Following the Administration of a Single Dose of 100 mg MK-8742 to Healthy Elderly Male and to Healthy Elderly Female Subjects

Pharmacokinetic Parameter	Healthy Elderly Female Subjects			Healthy Elderly Male Subjects			(Healthy Elderly Female Subjects/ Healthy Elderly Male Subjects)		rMSE‡
	n	GM	95% CI	n	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$† (µM•hr)	12	5.20	(3.52, 7.69)	12	3.91	(2.75, 5.57)	1.33	(0.83, 2.14)	0.562
C_{max}† (nM)	12	260	(174, 389)	12	201	(140, 289)	1.29	(0.79, 2.10)	0.577
C_{24}† (nM)	12	72.1	(48.9, 106)	12	55.1	(38.8, 78.2)	1.31	(0.82, 2.09)	0.557
t_{max}‖ (hr)	12	3.50	(2.99, 4.00)	12	3.02	(2.00, 4.01)			
Apparent terminal $t_{½}$§ (hr)	12	22.05	9.95	12	21.20	20.84			

Single oral dose of 100 mg (10 x 10 mg capsules) MK-8742 administered to healthy elderly males and females. †Back-transformed least-squares mean and confidence interval from ANOVA model containing fixed effect for population and continuous covariate for weight (P>0.05), and performed on natural log-transformed values; ‡rMSE: Square root of the residual variance component from the ANOVA model. rMSE*100% approximates the study %CV on the raw scale; ‖Median (min, max) reported for t_{max}; §Geometric mean and geometric CV are reported for apparent terminal $t_{½}$. GM = geometric least-squares mean; GMR = geometric least-squares mean ratio; CI = confidence interval.

Figure 2. Individual Plasma MK-8742 Ln-transformed $AUC_{0-\infty}$ Values vs Weight Following the Administration of a Single Dose of 100 mg MK-8742 Capsules in Healthy Elderly Males (n = 12) and Healthy Elderly Females (n = 12)



Weight: represent weight as assessed on Day -1 of Period 1

Conclusions

- The mean plasma $AUC_{0-\infty}$ following a single 100 mg dose of MK-8742 in healthy elderly female subjects is approximately 70% greater than that observed in healthy elderly male subjects. The mean plasma $AUC_{0-\infty}$ is approximately 33% greater in healthy elderly female subjects when adjusted for weight, suggesting that the observed gender effect may partially be explained by the difference in body weight.
- A single-dose 100 mg administration of MK-8742 results in similar $AUC_{0-\infty}$ values between healthy elderly male and healthy young male subjects, suggesting no effect of age on the pharmacokinetics of MK-8742.
- A single administration of 100 mg MK-8742 was generally well tolerated in the healthy elderly male and female subjects and healthy young male subjects in this study.

Disclosures

- This research was funded by Merck & Co., Inc., Whitehouse Station, NJ.
- WLM, WWY, LC, PJ, XH, DPD, HPF, and JRB are current employees of Merck & Co., Inc.

Contact Information

William Marshall, M.D.
Merck Research Laboratories
Merck & Co., Inc.
BMB3-421
33 Avenue Louis Pasteur
Boston, MA 02115
Phone: 617-992-3239
william.marshall@merck.com

Study Program for MK-5172/MK-8742

Current Phase 2b and Phase 2b/3 Special Population Studies

Study	Genotype	Fibrosis Staging	Treatment History	Comorbidity	Regimen (Weeks)
C-WORTHy	1	± Cirrhosis	TN, PR-PTF	±HIV	8, 12, 18, ±RBV
C-SCAPE	2, 4-6	Non-cirrhotic	TN	--	12, ±RBV
C-SALVAGE	1	± Cirrhosis	DAA/PR-PTF	--	12, + RBV
C-SURFER	1	Non-cirrhotic	TN	CKD 4-5	12, no RBV
C-SALT	1, 4-6	Cirrhotic (CP-B)	TN, PR-PTF	--	12, no RBV

Current Phase 3 Program

Study	Genotype	Fibrosis Staging	Treatment History	Comorbidity	Regimen (Weeks)
C-EDGE TN	1, 4-6	± Cirrhosis	TN	--	12, no RBV
C-EDGE CO-INFXN	1, 4-6	± Cirrhosis	TN	HIV	12, no RBV
C-EDGE CO-STAR	1, 4-6	± Cirrhosis	TN	OST, ±HIV	12, no RBV
C-EDGE TE	1, 4-6	± Cirrhosis	PR-PTF	±HIV	12 or 16, ±RBV

TN: Treatment Naïve; PR-PTF: Failed Prior Pegi-IFN/RBV; PI/PR-PTF: Failed Prior DAA/PR; CKD 4-5: Chronic Kidney Disease Grades 4-5 (incl. Hemodialysis); OST = Opiate Substitution Therapy; RBV = Ribavirin.

Presented at the 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, Washington DC; May 19-21, 2014.