Safety and Antiviral Activity of MK-5172, a Novel HCV NS3/4a Protease Inhibitor with Potent Activity Against Known Resistance Mutants, in Genotype 1 and 3 HCV-Infected Patients

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BACKGROUND

- MK-5172 is a novel, competitive inhibitor of the HCV NS3/4a protease with selective, potent in vitro activity against a broad range of HCV genotypes (GTs) and known viral variants that are resistant to other protease inhibitors in development.
- MK-5172 exhibits excellent selectivity over other serine proteases such as elastase and trypsin (no measurable inhibition), and shows only modest inhibitory potency with chymotrypsin (IC_{50} = 1.5 µM; 75,000-fold selective).
- In the genotype 1b replicon assay, MK-5172 potently inhibits viral replication (IC_{50} = 2 nM) and demonstrates a modest shift in the presence of 50% NHS (EC_{50} = 9.5 nM). In vitro, MK-5172 inhibits the NS3/4A enzyme from genotypes 1b, 2a, 2b, and 3a with K_i values of <0.02, 0.15, 0.02, and 0.7 nM, respectively. The genotype 2a replicon is also potently inhibited by MK-5172 (EC_{50} = 5 nM).

STUDY OBJECTIVES

- Assess the safety and tolerability of MK-5172 administered for 7 days to male patients infected with HCV genotypes (GT) 1 and 3.
- Evaluate the antiviral activity of MK-5172 administered as monotherapy for 7 days to male patients infected with either HCV GT 1 or 3.
- Evaluate the plasma pharmacokinetic profile of multiple oral doses of MK-5172 in HCV-infected patients.

STUDY DESIGN

- A double-blind, randomized, placebo-controlled study.
- Male patients 18-65 years of age with HCV RNA > 10^5 IU/mL and GT 1 or 3 chronic HCV infection without clinical evidence of cirrhosis.
- Patients received 400 mg of MK-5172 or placebo administered once daily (qd) fasted, for 7 consecutive days.
- One (1) out of the 6 patients in each panel received placebo instead of MK-5172 according to a randomized allocation schedule.
- Sampling for HCV viral RNA throughout the study.
- Patients followed for up to 2 months after the last dose.

METHODS

Safety Assessment

- Safety and tolerability were assessed by measurements of physical examination, vital signs, ECGs, and laboratory safety tests (CBC, chemistry panel, urinalysis).
- Adverse experiences were evaluated as to their intensity, seriousness, and possible relationship to study drug.

MK-5172 Analytical and Pharmacokinetic

- Plasma samples were analyzed for MK-5172 concentration using a validated HPLC-MS/MS assay with a lower limit of quantitation of 1.3 nM.
- C_{max}, T_{max}, and C_{24hr} were determined by visual inspection. $AUC_{0\text{-}24\ hr}$ was calculated using linear up/log down trapezoidal method.

MK-5172 Antiviral Efficacy

- Serial blood samples were collected throughout the study for evaluation of the plasma HCV RNA viral load using the Roche Cobas TaqMAN® 2.0 assay (lower limit of detection = 3.8 IU/mL).

Statistical Analysis

- A linear mixed-effects model was used with treatment, day, and the treatment-by-day interaction as fixed effects and with subject-within-treatment as a random effect.
- Profiles of the change from baseline in $\log_{10}$ HCV RNA are graphically displayed.

RESULTS

Subject Disposition

	GT1	GT3
Randomized: Total	6	6
Male (age range)	6 (22 to 54 yrs)	6 (25 to 65 yrs)
BMI (range)	25.9 (22.4 – 29.9)	22.6 (20.7 – 24.6)
Completed:	6	6
Discontinued:	0	0

Safety & Tolerability – Blinded Assessment

- No serious clinical or serious laboratory adverse experiences were reported.
- Eleven (11) patients reported a total of 21 clinical adverse experiences. The most commonly reported adverse experiences (reported by ≥2 patients) were headache, fatigue, and pruritus.
- Relationship to study drug has not yet been assessed as the study is still ongoing and therefore blinded to active vs placebo.
- No consistent treatment-related changes in laboratory values, vital signs, or ECG safety parameters were observed.
- Several patients on therapy showed transient reductions in liver function tests correlating with reductions in HCV RNA.

Pharmacokinetics

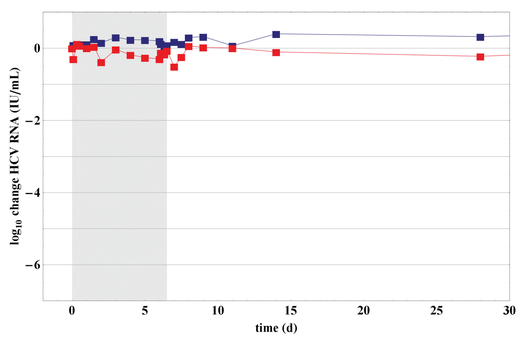
Preliminary Mean Plasma Pharmacokinetic Parameters Following Once Daily Administration of Multiple Oral Doses of MK-5172 for 10 Days to Healthy Male Subjects and 7 Days to Genotype 1 HCV-Infected Male Patients

		MK-5172 Dose		Pharmacokinetic Parameter				Apparent Half-life§
				AUC0-24hr†	Cmax†	C24 hr†	Tmax‡	
Panel	N	mg	Day	µM-hr	µM	µM	hr	hr
Healthy Subjects	6	400‖	1	2.18 ± 1.31	0.665 ± 0.74	15.1 ± 5.7	3.5 (3.0 – 6.0)	NA
			10	6.87 ± 2.43	1.95 ± 0.73	22.1± 6.0	3.0 (2.0 – 4.0)	20.7 ± 2.95
			AR	3.48 (1.96, 6.18)	4.47 (1.97, 10.14)	1.50 (1.09, 2.07)	NA	NA
HCV+ Patients	5	400#	1	10.38 ± 2.25	1.91 ± 0.91	85.5 ± 77.9	3.0 (2.0 – 6.0)	NA
			7	19.34 ± 13.05	3.47 ± 2.40	121.1 ± 108.3	3.0 (2.0 – 8.0)	29.9 ± 12.3
			AR	1.32 (0.70, 2.47)	1.24 (0.51, 3.05)	1.31 (0.92, 1.86)	NA	NA
HCV+/HS	NA	GMR	1	5.45 (2.56, 11.59)	4.27 (1.54, 11.85)	4.66 (2.40, 9.07)	NA	NA
			Last	2.06 (0.97, 4.38)	1.19 (0.43, 3.30)	4.05 (2.08, 7.87)	NA	NA

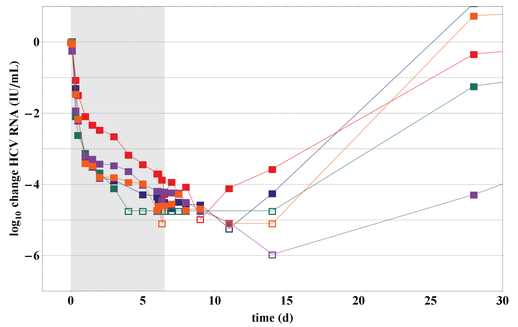
N = number
NA = Not applicable.
AR = Geometric Mean Ratio (Last Day/Day 1) with 90% confidence interval.
GMR = Geometric Mean Ratio (HCV+ Patients/Healthy Subjects) with 90% confidence interval.
† Mean ± SD.
‡ Median (Range).
§ Harmonic mean and pseudo SD.
‖ Dose was administered to healthy subjects qd on Days 1 - 10.
Dose was administered to HCV-infected patients qd on Days 1 – 7.

Antiviral Activity

Placebo: Individual Change from Baseline in $\log_{10}$ HCV RNA for Male Patients Who Received Placebo (N=2)

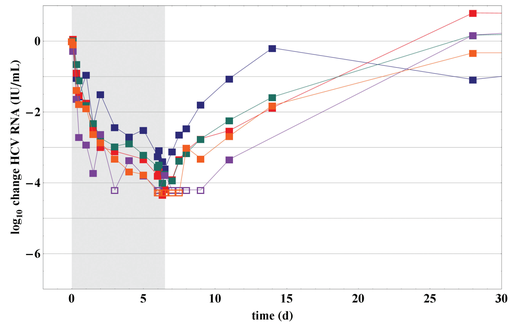


GT1a and GT1b: Individual Change from Baseline in $\log_{10}$ HCV RNA for Male Patients Who Received MK-5172 400 mg Once Daily for 7 Days (N=5)



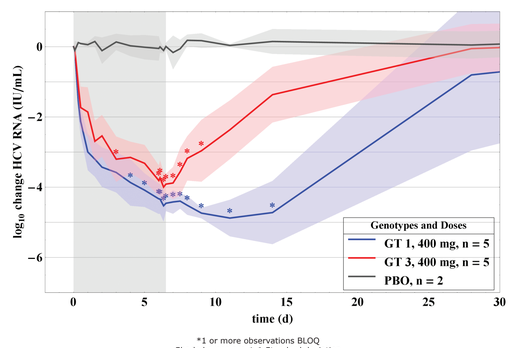
Open symbol indicates the observation is BLOQ

GT3: Individual Change from Baseline in $\log_{10}$ HCV RNA for Male Patients Who Received MK-5172 400 mg Once Daily for 7 Days (N=4)



Open symbol indicates the observation is BLOQ

Mean Change from Baseline in $\log_{10}$ HCV RNA for Male Patients Who Received MK-5172 400 mg Once Daily by Genotype or Matching Placebo for 7 Days



*1 or more observations BLOQ
Shaded areas are ± 1 Standard deviation

DISCUSSION

- Multiple oral doses of 400 mg MK-5172 qd for 7 days were generally well tolerated in HCV-infected patients.
- Mean maximum reductions from baseline of HCV viral RNA (Ses) were 5.4 (0.21) and 3.98 (0.22) $\log_{10}$ IU/mL for GT 1 and 3, respectively.
- No on-treatment related viral rebound was observed in any patient.
- Five GT 1 patients had decreases in HCV RNA to levels below the lower limit of detection during the study period.
- The mean time to nadir was more than 2 days after the last dose.
- By the 1 month follow-up visit, plasma levels of HCV RNA had returned to baseline levels for those patients for whom these data were available.
- Pharmacokinetic values of MK-5172 in HCV-infected patients were higher than values observed in healthy subjects (Petry, et al, Safety, tolerability and pharmacokinetics after single and multiple doses of MK-5172, a novel HCV NS3/4a protease inhibitor with potent activity against known resistance mutants, in healthy subjects. Poster # 1885, AASLD: The Liver Meeting 2010, Boston, MA, October 2010).

CONCLUSIONS

- MK-5172 exhibits potent antiviral activity during 7 days of monotherapy in patients with chronic GT1 and GT3 HCV-infections.
- Antiviral activity persisted for several days beyond the treatment period in GT1 patients.
- MK-5172 was generally well-tolerated with no serious adverse experiences, discontinuations due to adverse experiences, or safety laboratory abnormalities.
  - The current study is ongoing
  - Adverse experiences have not been unblinded
- These findings support further clinical investigation of MK-5172 for the treatment of chronic HCV-infection.

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