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

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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 against 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 Ki 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

- Evaluate the safety and tolerability of single-rising oral doses of MK-5172 administered to healthy male subjects in the fed and fasted state.
- Evaluate the safety and tolerability of multiple-rising oral doses of MK-5172 administered for 10 days to healthy male subjects.
- Evaluate the pharmacokinetic profile of MK-5172 (e.g., $AUC_{0-\infty}$, C_{max}, C_{12hr}, T_{max}, and apparent $t_{1/2}$) with single dose administration in the fasted state and following a standard high-fat breakfast to healthy male subjects.
- Evaluate the pharmacokinetic profile of MK-5172 (e.g., $AUC_{0-24\ hr}$, C_{max}, C_{24hr}, T_{max}, apparent $t_{1/2}$, and accumulation ratios) with multiple dose administration in healthy male subjects.

STUDY DESIGN

Single Rising-Dose Study

- A double-blind, placebo-controlled, alternating-panel, multiple-period study in young, healthy, male subjects (N=24).

Panel[§]	Period 1	Period 2	Period 3	Period 4	Period 5[‡]	Period 6
A[†]	2mg	10 mg	50 mg	200 mg	50 mg w/food	1200 mg
B[†]	5mg	25 mg	100 mg	400 mg	800 mg	
G[†#]	1200 mg	1600 mg	--	--	--	--

[§]Subjects were randomized to receive single oral doses of MK-5172 (n=6) or matching placebo (n=2) according to a computer-generated allocation schedule.
[†]The assigned treatment in Periods 3 and 5 of Panel A were the same such that the same subjects received active drug or placebo in both periods.
[‡]Different subjects participated in each panel.
[#]There will be at least a 7 day washout period between Period 1 and Period 2.

- For Panel A Period 3, the same 2 subjects who received placebo also received placebo for their repeat dose in treatment Period 5. This permitted an intra-subject comparison of the effect of food on the pharmacokinetic profile of MK-5172.

Multiple Rising-Dose Study

- A double-blind, randomized, placebo-controlled, serial-panel, rising-dose study in young, healthy, male subjects (N=40).
- Five panels (Panels C, D, E, F, and H) consisted of 8 subjects each who received 100, 200, 400, 700, and 1000 mg of MK-5172 or placebo administered once daily (qd) fasted, for 10 consecutive days.
- Two out of the 8 subjects in each panel received placebo instead of MK-5172 according to a randomized allocation schedule.

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}, C_{12hr} and C_{24hr} were determined by visual inspection.
- $AUC_{0-\infty}$ and $AUC_{0-24\ hr}$ were calculated using linear up/log down trapezoidal method.

Statistical Analysis

- For the single dose portion of the study, a linear mixed-effects model was used with fixed effect for treatment and a random effect for subject.
- For the multiple dose portion of the study, a linear mixed-effects model was used with fixed effects for dose, day, and dose-by-day interaction, and subject-within-dose as a random effect.
- Natural –log transformation was performed for C_{12hr}, C_{24hr}, C_{max}, $AUC_{0-\infty}$, and $AUC_{0-24\ hr}$ before analysis.

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RESULTS

Subject Disposition

	Single Dose	Multiple Dose
Randomized: Total	25	41
Male (age range)	25 (19 to 44 yrs)	41 (19 to 45 yrs)
Completed:	24	40
Discontinued:	1[†]	1[‡]

[†]Withdrew consent for reasons unrelated to the study.
[‡]Discontinued due to a flu-like illness considered "definitely not" related to MK-5172 by the investigator.

Safety & Tolerability – Blinded Assessment

- No serious clinical or serious laboratory adverse experiences were reported.
- Single-Rising Dose Study: 23 subjects reported a total of 72 clinical adverse experiences. The most commonly reported adverse experiences (reported by ≥2 subjects) were headache, fatigue, dizziness, disturbance in attention, abdominal pain, nausea, loose stool, diarrhea, oropharyngeal pain, and throat irritation.
- Multiple-Rising Dose Study: 27 subjects reported a total of 56 clinical adverse experiences. The most commonly reported adverse experiences (reported by ≥2 subjects) were headache, dizziness, abdominal pain, nausea, loose stool, diarrhea, nasopharyngitis, and flu-like illness.
- Relationship to study drug has not yet been assessed as the study is still blinded to active vs. placebo.
- No consistent treatment-related changes in laboratory values, vital signs, or ECG safety parameters were observed.

Pharmacokinetics

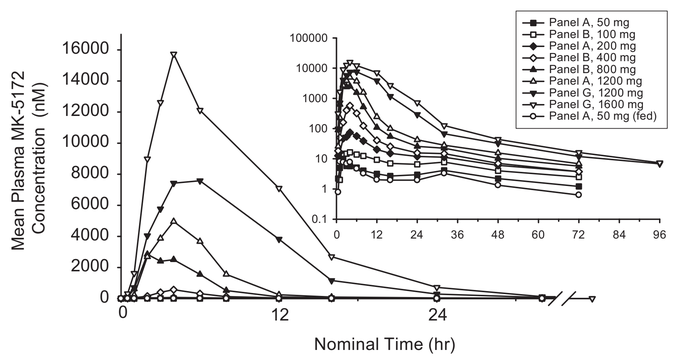
- Single-Rising Dose Study

Preliminary Results - MK-5172 Mean (SD) Plasma Pharmacokinetic Parameters Following Administration of Single Oral Doses in Healthy Male Volunteers

Dose (mg)	N	AUC_{0-inf} (hr*µM)	C_{max} (nM)	C_{12} (nM)	C_{24} (nM)	T_{max}[a] (hr)	$t_{1/2}$[b] (hr)
25	6	-	3.3 ± 1.2	-	-	2.5 (2.0, 6.0)	-
50	6	0.289 ± 0.110	12.3 ± 6.4	3.2 ± 1.2	3.0 ± 1.2	2.0 (1.0, 4.0)	34.4 ± 7.8
100	6	0.549 ± 0.184	24.5 ± 10.9	9.2 ± 7.1	6.6 ± 3.0	3.5 (2.0, 6.0)	27.2 ± 8.0
200	6	1.15 ± 0.203	83.4 ± 24.8	20.2 ± 4.7	11.9 ± 3.5	4.0 (2.0, 6.0)	25.7 ± 4.9
400	6	3.29 ± 2.16	597 ± 576	40.8 ± 18.8	15.6 ± 6.7	4.0 (2.0, 6.0)	20.6 ± 4.0
800	6	15.1 ± 7.87	4235 ± 2957	115 ± 34.5	26.5 ± 6.74	4.0 (2.0, 6.0)	18.9 ± 5.0
1200	6	27.6 ± 20.8	5850 ± 3218	158 ± 95.8	39.2 ± 15.9	4.0 (2.0, 6.0)	19.7 ± 2.3
1200[†]	6	53.6 ± 50.1	8610 ± 7110	1160.1 ± 1958.5	67.4 ± 57.6	5.0 (4.0, 6.0)	15.0 ± 1.3
1600	6	105.0 ± 869.0	17200 ±14000	2693.7 ± 2960.2	125.4 ± 94.6	4.0 (2.0, 6.0)	16.0 ± 5.6
50 (fed)	6	0.220 ± 0.114	16.7 ± 12.9	2.4 ± 0.69	2.32 ± 0.68	3.0 (1.0, 4.0)	34.4 ± 7.8

[a]Median (Min, Max); [b]Harmonic Mean ± Pseudo SD
[†]Repeat dose in different group of subjects.

Preliminary Results – MK-5172 Protocol 001
Mean Plasma Concentration Profiles for Subjects Administered Single Oral Doses (50- to 1600-mg) of MK-5172 in the Fed and Fasted State in Healthy Male Subjects (Inset: log-scale; LOQ = 1.3 nM)



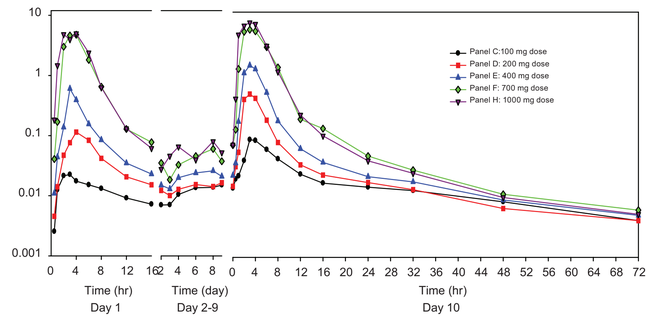
Multiple-Rising Dose Study

Preliminary Results – MK-5172 Protocol 001
Mean Plasma Pharmacokinetic Parameters Following Once Daily Administration of Multiple Oral Doses of MK-5172 for 10 Days to Healthy Male Subjects (N=6/dose)

Dose	Day	Pharmacokinetic Parameter: AUC_{0-24hr}[a]	C_{max}[a]	$C_{24\ hr}$[a]	T_{max}[b]	Apparent Half-life[c]
mg		*µM-hr*	*µM*	*nM*	*hr*	*hr*
100	1	0.258 ± 0.129	0.026 ± 0.011	7.03 ± 2.47	3.0 (2.0 - 4.0)	NA
	10	0.797 ± 0.456	0.099 ± 0.104	14.7 ± 5.52	4.0 (3.0 - 6.0)	24.5 ± 2.87
	GMR	3.0	3.0	2.1	NA	NA
200	1	0.802 ± 0.567	0.146 ± 0.16	12.3 ± 4.29	4.0 (2.0 - 6.0)	NA
	10	2.561 ± 1.76	0.710 ± 0.677	17.5 ± 5.37	4.0 (2.0 - 4.0)	20.6 ± 3.91
	GMR	3.2	5.1	1.5	NA	NA
400	1	2.176 ± 1.305	0.665 ± 0.737	15.1 ± 5.7	3.5 (3.0 - 6.0)	NA
	10	6.866 ± 2.432	1.954 ± 0.729	22.1 ± 6.0	3.0 (2.0 - 4.0)	20.7 ± 2.95
	GMR	3.5	4.5	1.5	NA	NA
700	1	20.637 ± 15.198	5.299 ± 3.982	35.2 ± 11.9	3.0 (2.0 - 4.0)	NA
	10	32.806 ± 27.314	6.965 ± 4.361	48.4 ± 34.1	2.5 (2.0 - 4.0)	17.1 ± 5.5
	GMR	1.5	1.5	1.1	NA	NA
1000	1	23.882 ± 14.788	6.854 ± 4.099	27.7 ± 8.6	4.0 (2.0 - 6.0)	NA
	10	40.787 ± 28.744	9.428 ± 5.789	40.3 ± 13.3	3.0 (2.0 - 4.0)	16.7 ± 2.9
	GMR	1.7	1.4	1.4	NA	NA

Note: Dose was administered q.d. on Days 1 through 10; NA - Not applicable; GMR - Geometric Mean Ratio (Day 10/Day 1);
[a]Mean ± SD; [b]Median (Range); [c]Harmonic mean and pseudo SD

Preliminary Results – MK-5172 Protocol 001
Mean Plasma Profiles Following Once Daily Administration of Multiple Oral Doses of MK-5172 for 10 Days to Healthy Male Subjects (N=6/dose)



DISCUSSION

- Single doses (2 to 1600 mg) and multiple oral doses (100 to 1000 mg qd for 10 days) of MK-5172 were generally well tolerated in healthy male subjects.

Single-Rising Dose Study

- Following oral administration, MK-5172 increased in plasma with median T_{max} values of 2.0 – 5.0 hours. Therefore, concentrations declined in a biphasic manner with mean terminal $t_{1/2}$ ~15.0 – 34.4 hours.
- Administration of 50 mg with a high-fat meal had no clinically meaningful effect on plasma MK-5172 pharmacokinetic values.
- Mean $AUC_{0-\infty}$, C_{max}, and C_{24hr} values appeared to increase in a dose proportional fashion through 200 mg and in greater than dose proportional manner at doses greater than 200 mg.

Multiple-Rising Dose Study

- Steady state was achieved after approximately 6 days. At steady state, approximately 3-fold accumulation of plasma MK-5172 with respect to $AUC_{0-24\ hr}$ and C_{max} were observed for doses of 100 – 400 mg.
- At higher doses, the extent of accumulation was less (~1.5-fold) for $AUC_{0-24\ hr}$ and C_{max} due to a greater contribution of $AUC_{0-24\ hr}$ to the overall exposure.
- The $C_{24\ hr}$ geometric mean accumulation ratio (Day 10/Day 1) was approximately 1.5 for most dose levels.
- Mean $AUC_{0-24\ hr}$ and C_{max} appeared to increase in a greater than dose proportional manner at steady-state.
- The median T_{max} (2.5 – 4.0 hours) and apparent $t_{1/2}$ (~20 hours) of MK-5172 on Day 10 after once daily dosing were consistent with values from the single-dose portion of the study.

CONCLUSION

- MK-5172 is generally well tolerated and exhibits a pharmacokinetic profile supportive of once daily dosing.

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