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 proteases. The effects of other serine proteases were not evaluated.

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 ($\text{IC}_{50} = 1.5 \mu M$).

In the genotype 1 replicase assay, MK-5172 inhibited viral replication ($\text{IC}_{50} = 2 \mu M$) and demonstrated a modest shift in the presence of SDR, NLR ($\text{IC}_{50} = 0.3 \mu M$). In vitro, MK-5172 inhibits the GT 1a replicase in the range of 0.1, 0.5, and 2.5 nM, and is 100-fold selective for in vitro inhibition of GT 2a, 2b, and 3a with K values of 0.02, 0.05, and 0.07, respectively.

The genotypic 2a replicase is also partially inhibited by MK-5172 ($\text{IC}_{50} = 3 \mu M$).

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 other HCV GT (GT 2 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) 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 3 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 0.3 nM.
- $C_{\text{min}}$, $T_{\text{max}}$, and $C_{\text{max}}$ were determined by visual inspection. $AUC_{\text{last}}$ was calculated using linear up/log down trapezoidal method.

MK-5172 Antiviral Efficacy

- Serial plasma samples were collected throughout the study 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

Safety & Tolerability – Blinded Assessment

- No severe clinical or serious laboratory adverse experiences were reported.
- Eleven (11) patients reported a total of 21 clinical adverse experiences.
- 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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Week</th>
<th>Ceremony</th>
<th>Phase</th>
<th>Treatment</th>
<th>Drugs</th>
<th>Mean Plasma Pharmacokinetic Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$C_{\text{min}}\mu M$ $T_{\text{max}}\text{hr}$ $C_{\text{max}}\mu M$ AUC_{\text{last}}\mu M \cdot \text{hr}$ $C_{\text{area}}\mu M$ $AR$</td>
</tr>
<tr>
<td>Healthy</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.033 ± 0.056 0.04 ± 0.07 0.05 ± 0.07 0.033 ± 0.056 0.05 ± 0.07 1.00 (0.59, 1.82)</td>
</tr>
<tr>
<td>Subjects</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.033 ± 0.056 0.04 ± 0.07 0.05 ± 0.07 0.033 ± 0.056 0.05 ± 0.07 1.00 (0.59, 1.82)</td>
</tr>
</tbody>
</table>

AR = Geometric Mean Ratio (Last Day/Day 1) with 90% confidence interval.

N = number.

Safety & Tolerability – Unblinded Assessment

- No serious clinical or serious laboratory adverse experiences were reported.
- Five (5) patients had decreases in HCV RNA totaling $\leq 0.5$ log_{10} IU/mL.
- The current study is ongoing.
- The mean time to nadir was more than 2 days after the last dose.
- By the 1st 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 the 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 experience, 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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