MK-7009 Significantly Improves Rapid Viral Response (RVR) in Combination with Pegylated Interferon Alfa-2a and Ribavirin in Patients with Chronic Hepatitis C (CHC) Genotype 1 Infection

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Background
The rate of virologic cure (SVR) associated with pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy in patients with chronic hepatitis C (CHC) genotype 1 infection, long treatment duration (48 weeks), and significant side effects ofpegylated interferon and ribavirin therapy highlight the need for new therapies.

MK-7009 is a non-competitive inhibitor of HCV NS3/4A protease, with demonstrated safety and efficacy when administered as monotherapy for 8 days.

We now present the primary analysis results from an ongoing Phase IIa study of MK-7009 for 28 days in combination with pegylated-interferon and ribavirin (peg-IFN/RBV).

Methods

Study Design
- A randomized, placebo-controlled, double-blind study of MK-7009 in treatment naïve patients with CHC genotype 1 infection.

MK-7009 was administered for 28 days with peg-IFN/RBV in 15/19 patients evaluated.

Patients with RVR rates for at least 1 MK-7009-treated group superior to lower limit of quantification (LLOQ) of 25 IU/mL.

HCV RNA was measured by Roche Cobas Taqman which has a lower limit of detection (LLOD) of 10 IU/mL, and a lower limit of quantification (LLOQ) of 25 IU/mL.

Primary hypothesis
- RVR rates for at least 1 MK-7009-treated group superior to placebo.

Acceptable safety and tolerance of MK-7009 compared with placebo.

Results

Table 1. Baseline Patient Characteristics – All Treated Patients

<table>
<thead>
<tr>
<th>Key Parameter</th>
<th>Placebo†</th>
<th>Placebo*</th>
<th>MK-7009 300 mg bid*</th>
<th>MK-7009 600 mg bid*</th>
<th>MK-7009 600 mg qd*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F) (%)</td>
<td>15/19</td>
<td>16/20</td>
<td>17/17</td>
<td>16/20</td>
<td>17/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 44 44 44 46</td>
<td>46 46 44 44 46</td>
<td>48 46 44 44 46</td>
<td>46 46 44 44 46</td>
<td>48 46 44 44 46</td>
</tr>
<tr>
<td>Race (%)</td>
<td>3 1 4 2 1 2 8 3 5 4 2</td>
<td>3 1 4 2 1 2 8 3 5 4 2</td>
<td>3 1 4 2 1 2 8 3 5 4 2</td>
<td>3 1 4 2 1 2 8 3 5 4 2</td>
<td>3 1 4 2 1 2 8 3 5 4 2</td>
</tr>
<tr>
<td>Hemoglobin (%)</td>
<td>80 78 78 78 78</td>
<td>78 78 78 78 78</td>
<td>78 78 78 78 78</td>
<td>78 78 78 78 78</td>
<td>78 78 78 78 78</td>
</tr>
<tr>
<td>Platelet (%)</td>
<td>37 37 37 37 37</td>
<td>37 37 37 37 37</td>
<td>37 37 37 37 37</td>
<td>37 37 37 37 37</td>
<td>37 37 37 37 37</td>
</tr>
</tbody>
</table>

Efficacy

Table 2. Percent of Subjects with RVR (Virologic Failure) (Table 2)

<table>
<thead>
<tr>
<th>MK-7009 Dose</th>
<th>Peg-IFN/RBV</th>
<th>50% RVR/Pts.</th>
<th>&lt;0.0001 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo†</td>
<td>15/19</td>
<td>15/19</td>
<td>15/19</td>
</tr>
<tr>
<td>MK-7009 300 mg bid*</td>
<td>16/20</td>
<td>44</td>
<td>11.1</td>
</tr>
<tr>
<td>MK-7009 600 mg bid*</td>
<td>17/17</td>
<td>48</td>
<td>16.7</td>
</tr>
<tr>
<td>MK-7009 600 mg qd*</td>
<td>17/17</td>
<td>50</td>
<td>22.2</td>
</tr>
</tbody>
</table>

SVR

MK-7009 showed potent antiviral effect at all dose levels tested.
- Viral suppression maintained after MK-7009 dosing ended, through Day 42.
- Similarly high rates of SVR in all MK-7009 groups.
- Dose-differentiation limited by small sample size.

MK-7009 was generally well-tolerated with no serious adverse events and no adverse events leading to discontinuation.
- Incidence of vomiting appears higher in 600 mg bid dose group.
- Most events were short duration, of mild intensity, and no anti-emetics were required.

These results support further development of MK-7009 as an anti-HCV treatment.

Figure 3. Virologic Failure (per-protocol Population)

Mark J. Popovick, MD

Figure 2. Percent of Per-protocol Patients with HCV RNA Below LOQ (≥25 IU/mL) and HCV RNA Below LOQ (≥10 IU/mL) by Treatment Group

Efficacy

Table 3. Most Common Adverse Experiences with Onset during MK-7009 Treatment and 14-Day Follow-Up (incidence ≥10% in One or More Treatment Groups)

<table>
<thead>
<tr>
<th>Key Adverse Event</th>
<th>Placebo†</th>
<th>Placebo*</th>
<th>MK-7009 300 mg bid*</th>
<th>MK-7009 600 mg bid*</th>
<th>MK-7009 600 mg qd*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients with Onset during MK-7009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache (%)</td>
<td>10.5</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>10.5</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Fatigue (%)</td>
<td>10.5</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Influenza-like Illness (%)</td>
<td>10.5</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
</tr>
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MK-7009 Dose
- MK-7009 Dose 300 mg bid
- MK-7009 Dose 600 mg bid
- MK-7009 Dose 600 mg qd

RVR/Pts.
- RVR/Pts. Placebo†
- RVR/Pts. MK-7009 300 mg bid*
- RVR/Pts. MK-7009 600 mg bid*
- RVR/Pts. MK-7009 600 mg qd*

Safety
- No adverse events and no discontinuations due to an adverse event were reported.
- The most common adverse events reported were headache, nausea, fatigue, and influenza-like illness, which were reported at similar rates between all treatment groups, including placebo (Table 3).
- The incidence of nausea and vomiting appeared to be higher in the MK-7009 treatment groups compared to placebo (Table 3).
- No clinically significant changes in ECGs were observed.

Study Acknowledgments
- The authors would like to thank the patients who participated in this study, and all the investigators, site staff, and Merck colleagues who supported the study.

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Study Design
- A randomized, placebo-controlled, double-blind study of MK-7009 (all doses) in HCV infection treatment naïve patients with CHC genotype 1 infection.

All patients continued peg-IFN/RBV for an additional 44 weeks.

Figure 3. Virologic Failure (per-protocol Population)

Summary

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Primary hypotheses
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- With no adverse events and no discontinuations due to an adverse event were reported.
- The most common adverse events reported were headache, nausea, fatigue, and influenza-like illness, which were reported at similar rates between all treatment groups, including placebo (Table 3).
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