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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 low rate of virologic cure [40-50% sustained virologic response (SVR) of genotype 1 HCV], long treatment duration (48 weeks), and significant side effects of pegylated interferon and ribavirin therapy highlight the pressing medical need for advancement in anti-HCV therapy.
- MK-7009 is a non-covalent 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 from an ongoing Phase IIa study of MK-7009 for 28 days in combination with pegylated-interferon and ribavirin (peg-IFN/RBV).

Methods

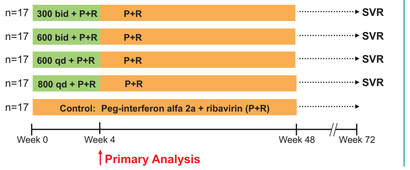
Study Design

- A randomized, placebo-controlled, double-blind study of MK-7009 in treatment-naïve patients with chronic genotype 1 HCV infection.
- MK-7009 was administered for 28 days with peg-IFN/RBV in 1 of 5 regimens: placebo, 300 mg bid, 600 bid, 600 mg qd, or 800 mg qd.
- All patients continued peg-IFN/RBV for an additional 44 weeks.
- The primary endpoint was the percent of subjects with viral suppression to below the lower limit of detection at day 28 (rapid viral response or RVR).
- 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 hypotheses

- RVR rates for at least 1 MK-7009-treated group superior to placebo.
- Acceptable safety and tolerability of MK-7009 compared with placebo.

Figure 1. Study Design



Patient Population

- Key Inclusion Criteria:
  - Chronic, compensated genotype 1 HCV infection
  - HCV RNA ≥400,000 IU/mL at screening
  - Treatment-naïve
- Key Exclusion Criteria:
  - Non-HCV-related chronic hepatitis
  - HIV co-infection
  - Evidence of cirrhosis on liver biopsy or approved non-invasive imaging
  - Any other condition contraindicated for treatment with peg-IFN/RBV

Data Analysis

- **Safety analysis based on the All-patients-as-treated population**
- **Reasons for exclusion from Per-protocol (PP) population:**
  - Taking a restricted concomitant medicine
  - Missing more than the allowed number of doses for MK-7009/ placebo, peg-IFN, or RBV
- **Statistical Definition of Superiority for RVR rates:**
  - (Lower bound of 95% CI of [MK-7009 group RVR – placebo group RVR]) >0
- **Protocol-defined Virologic Failure:**
  - Relapse: a >1 log increase from nadir at two consecutive measurements, or HCV RNA >100 IU/mL on 2 measurements after LLOD
  - Nonresponder: ≤2 log decrease through Day 28
- Because the study is ongoing, some data points are subject to change by the time the final study report is submitted

Viral Resistance: Population Sequencing of NS3/4A gene

- DNA Amplicons obtained at baseline and the indicated failure time points were purified and subjected to DNA-sequence analysis.
- For technical reasons, population sequence analysis could only be performed on patient samples with >1000 IU/mL HCV RNA.

Summary

- MK-7009 showed potent antiviral effect at all doses tested.
  - Viral suppression maintained after MK-7009 dosing ended, through Day 42
  - Similarly high rates of RVR in all MK-7009 treatment 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.

Results

Patient Population

- 95 patients with no prior treatment for HCV infection were randomized to 1 of 5 groups [placebo and 4 dose groups of MK-7009 (**Table 1**)].
- One patient withdrew consent after screening and did not receive any study therapy after randomization. This patient was excluded from all analyses.

Table 1. Baseline Patient Characteristics − All Treated Patients

Parameter	MK-7009 300 mg bid + P+R (N=18)	MK-7009 600 mg bid + P+R (N=20)	MK-7009 600 mg qd + P+R (N=18)	MK-7009 800 mg qd + P+R (N=19)	Placebo + P+R (N=19)	Total (N=94)
Female %	22	45	61	38	42	42
Median Age (years)	46	44	51	44	46	45
Age Range (years)	27 to 65	22 to 58	34 to 64	21 to 65	32 to 65	21 to 65
Race: Asian %	6	5	11	11	11	9
Black %	11	15	11	5	11	11
Multi-Racial %	-	-	-	-	11	2
Pacific Islander %	6	-	6	-	5	3
White %	78	80	72	84	63	76
HCV GT1 nontypeable %	17	15	17	21	11	16
HCV GT 1a %	33	40	39	42	42	39
HCV GT 1b %	50	45	44	37	47	44

Efficacy (Table 2)

- RVR rates in MK-7009-containing arms ranged from 69% to 82% vs. 6% of the control (per-protocol population).
- MK-709 RVR rates were similar for the full analysis set population (range, 71 to 83%).
- All of the MK-7009 dose groups were superior to control (p<0.0001), satisfying the primary efficacy hypothesis.

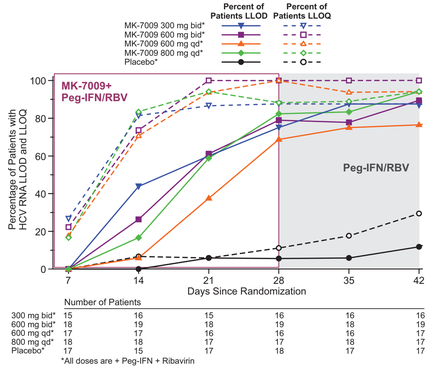
Table 2. Percent of Subjects with Rapid Viral Response (RVR)

MK-7009 Dose Group	Per-protocol Population: Pts. w RVR/Pts. Treated	Per-protocol Population: % RVR	Per-protocol Population: P-value (vs. pbo)	Full Analysis Set: Pts. w RVR/Pts. Treated	Full Analysis Set: % RVR	Full Analysis Set: P-value (vs. pbo)
300 mg bid	12/16	75.0	<0.0001	12/17	70.6	<0.0001
600 mg bid	15/19	78.9	<0.0001	16/20	80.0	<0.0001
600 mg qd	11/16	68.8	<0.0001	12/17	70.6	<0.0001
800 mg qd	14/17	82.4	<0.0001	15/18	83.3	<0.0001
Placebo	1/18	5.6	n/a	1/19	5.3	n/a

Efficacy

- **Percent of Subjects LLOD and LLOQ (Figure 3):**
- Greater than 80% of subjects treated with MK-7009 (all doses) had viral suppression to below LLOD on Day 28.
- Viral suppression continued after MK-7009 was stopped, with 77 to 94% of subjects below LLOD on Day 42.
- 100% of subjects in the 600 mg bid MK-7009 dose group were below LLOQ from Day 21 through 42.

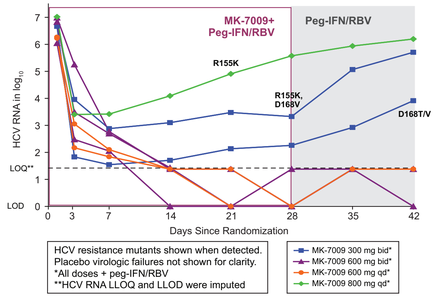
Figure 2. Percent of Per-Protocol Patients with HCV RNA Below LLOQ (<25 IU/mL) and Below LLOD (<10 IU/mL) by Treatment Group



Efficacy

- **Protocol-defined Virologic Failures (Figure 3)**
  - Through day 42, patients in 600 mg qd and 600 mg bid groups who met criteria failure (Methods) did not have sufficient level of HCV RNA to perform resistance analysis (<1000 IU/mL). As a result, no resistance mutations were detected.
  - Virologic failure was observed in 300 mg bid and 800 mg qd groups, with detection of HCV mutations known to confer resistance to MK-7009.
  - Current studies are focused on understanding the evolution of resistance via longitudinal analysis of patient samples throughout the MK-7009 dosing period.
  - In addition, amplicons will be subjected to clonal analysis to identify possible linkage between the observed mutants (i.e., R155K and D168V).

Figure 3. Virologic Failures (Per-protocol Population)



Safety

- No serious adverse events and no discontinuations due to an adverse event were observed during the first 42 days.
- The most common adverse events reported were headache, nausea, fatigue, and influenza-like illness, which were reported at similar rates across 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 increase in rash adverse events over placebo were observed.
- No clinically significant changes in ECGs were observed.

Table 3. Most Common Adverse Experiences with Onset during MK-7009 Treatment and 14-Day Follow-Up (Incidence >20% in One or More Treatment Groups)

	MK-7009 300 mg bid + Peg-IFN + RBV (N=18)		MK-7009 600 mg bid + Peg-IFN + RBV (N=20)		MK-7009 600 mg qd + Peg-IFN + RBV (N=18)		MK-7009 800 mg qd + Peg-IFN + RBV (N=19)		Placebo + Peg-IFN + RBV (N=19)	
Event Category	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:										
With one or more adverse experiences	15	(83.3)	18	(90.0)	16	(88.9)	17	(89.5)	17	(89.5)
With no adverse experience	3	(16.7)	2	(10.0)	2	(11.1)	2	(10.5)	2	(10.5)
With specific adverse experiences										
Anorexia	3	(16.7)	5	(25.0)	2	(11.1)	1	(5.3)	2	(10.5)
Diarrhea	1	(5.6)	5	(25.0)	2	(11.1)	4	(21.1)	4	(21.1)
Dyspepsia	4	(22.2)	0	(0.0)	2	(11.1)	3	(15.8)	4	(21.1)
Fatigue	3	(16.7)	7	(35.0)	3	(16.7)	1	(5.3)	6	(31.6)
Headache	5	(27.8)	9	(45.0)	8	(44.4)	3	(15.8)	7	(36.8)
Influenza-like illness	4	(22.2)	4	(20.0)	4	(22.2)	5	(26.3)	3	(15.8)
Nausea	5	(27.8)	8	(40.0)	7	(38.9)	6	(31.6)	5	(26.3)
Rash	2	(11.1)	2	(10.0)	3	(16.7)	2	(10.5)	4	(21.1)
Vomiting	0	(0.0)	8	(40.0)	3	(16.7)	3	(15.8)	1	(5.3)

N = Number of randomized and treated patients in each treatment group.
Although a patient may have had two or more adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Summary of reported adverse experiences of vomiting (600 mg bid MK-7009)

- Day of onset: 1, 4, 5, 10, 16, 18, 20, 21.
- Duration: from 1d to 23d.
- 4 out of 8 subjects had vomiting of 1 day or less in duration.
  - In 1 subject, vomiting routinely coincided with MK-7009 administration (Day 5 to 28)
- Vomiting did not require anti-emetic treatment and did not lead to discontinuation, or dose reduction of MK-7009.

Laboratory trends over the treatment period showed:

- Decreasing and/or stable liver transaminase levels
- Mean decreases in hemoglobin and absolute neutrophil count for MK-7009 groups similar to placebo

Acknowledgments

Data Safety Monitoring Board

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