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A phase 2B study of MK-7009 (vaniprevir) in patients with genotype 1 HCV infection who have failed previous pegylated interferon and ribavirin treatment

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Background & Aims: MK-7009 (vaniprevir) is a non-covalent competitive inhibitor of the hepatitis C virus (HCV) NS3/4A protease. This report presents the primary analysis results (safety and sustained viral response) of a phase 2b study of MK-7009 given in combination with peginterferon (PegIFN) alfa2a 180 μg weekly and ribavirin (RBV) 1000–1200 mg/day, for 24–48 weeks to non-cirrhotic patients who have failed previous PegIFN and RBV treatment.

Methods: We present results of a randomized, placebo-controlled, double-blind study of MK-7009 administered for 24–48 weeks in combination with PegIFN and RBV in 4 regimens to at least 40 patients per arm. Stratification by prior response to PegIFN and RBV was as follows: null response, partial response, breakthrough and relapse. HCV RNA was determined by Roche Cobas Taqman with a lower limit of detection (LLoD) of 10 IU/ml and a lower limit of quantification (LLoQ) of 25 IU/ml.

Results: SVR_{24} in patients on MK-7009 + PegIFN and ribavirin (P/R) was statistically superior to placebo + P/R in all treatment groups ($p <0.001$). MK-7009 at 300 mg b.i.d. and 600 mg b.i.d. is generally well tolerated for use for up to 48 weeks of therapy. Patients in MK-7009 regimens had higher rates of gastrointestinal adverse events as compared to control (mostly mild to moderate). There were no significant differences in rates of anemia and rash between the MK-7009 regimens and control.

Conclusions: In conclusion, patients treated with MK-7009 plus P/R experienced significant improvement in SVR compared to P/R control in a population of GT 1 experienced patients.

Introduction

Hepatitis C virus (HCV) is a positive-strand RNA virus of the Flaviviridae family and replicates primarily in the liver. While disease progression is typically a slow process that occurs over many years, a significant fraction of patients ultimately develop serious liver disease, including cirrhosis and hepatocellular carcinoma [1].

Multiple viral proteins essential for HCV replication have been characterized [1,2] and clinical proof of concept has been demonstrated for small-molecule inhibitors that act against several of these, including NS3/4A protease [3,4], NS5B polymerase (both active site and allosteric inhibitors) [5–8], NS4A [9], and most recently, NS5A [10]. Of these, NS3/4A protease inhibitors have progressed the furthest in terms of clinical evaluation and have been demonstrated to achieve highly significant reductions in HCV viral loads in patients [11].

Until recently, standard treatment for HCV infection was combination therapy with pegylated interferon and ribavirin (P/R) [12–14]. However, recent FDA approval of the directly acting antiviral agents boceprevir [15,16] and telaprevir [17,18] has added to the HCV treatment armamentarium. These compounds have been added to the previous P/R backbone in genotype 1 infected patients to create a 3-drug treatment regimen. Both boceprevir and telaprevir are orally bioavailable α ketoamide NS3/4A protease inhibitors that reversibly and covalently bind to the HCV protease. A sustained virological response (SVR) of up to 70% is observed when either of these protease inhibitors is utilized with P/R and ribavirin in treatment naive patients [19]. Both agents are also effective in patients who failed to achieve SVR during previous treatment with P/R, though overall SVR rates are generally lower.

In addition to the already approved HCV protease inhibitors, there are several other investigational second-wave NS3/4A protease inhibitors. Vaniprevir (MK-7009) is one such compound and is a macrocyclic HCV NS3/4A protease inhibitor which has demonstrated potent antiviral efficacy and good tolerability in a

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14-day phase I monotherapy trial as well as a phase II dose-ranging study [20].

This manuscript presents the primary analysis results (safety and sustained viral response) of a phase 2b study of MK-7009 given in combination with PegIFN 180 µg weekly and RBV 1000–1200 mg/day for 24–48 weeks, to non-cirrhotic patients who have failed previous P/R treatment.

Materials and methods

Study design

MK-7009 safety and efficacy had been established in a phase 2A study of treatment naïve patients (MK-7009 study 007) [20]. The data presented in this report are from a randomized, placebo-controlled, double-blind study of MK-7009 administered for 24 or 48 weeks to non-cirrhotic patients, who failed previous P/R treatment, enrolled from Australia, Austria, Belgium, Canada, Chile, Czech Republic, France, Germany, Israel, Korea, Lithuania, New Zealand, Poland, South Korea, Sweden, Taiwan, Thailand, UK, and the USA. Patients were treated with MK-7009 for longer durations in the current study when compared to MK-7009 study 007 with the assumption that the demonstration of safety and efficacy in a treatment experienced population would imply safety and efficacy in a treatment naïve population. The study was conducted in accordance with principles of Good Clinical Practice and the Declaration of Helsinki and was approved by the appropriate institutional review boards and regulatory agencies. Informed consent was documented for each patient prior to study enrollment.

Patient safety was overseen by an external Data Monitoring Committee made up of 4 internationally recognized hepatologists and/or infectious disease specialists and one statistician. The committee met quarterly at a minimum to discuss safety and efficacy. Additionally, direct patient monitoring for safety by principal investigators included patient history, physical exams and pre-specified laboratory safety evaluations at study visits on days 1, 3 and 7 for the first week, weekly from weeks 2 through 4, every other week from weeks 5 through 12 and then monthly through end of study treatment.
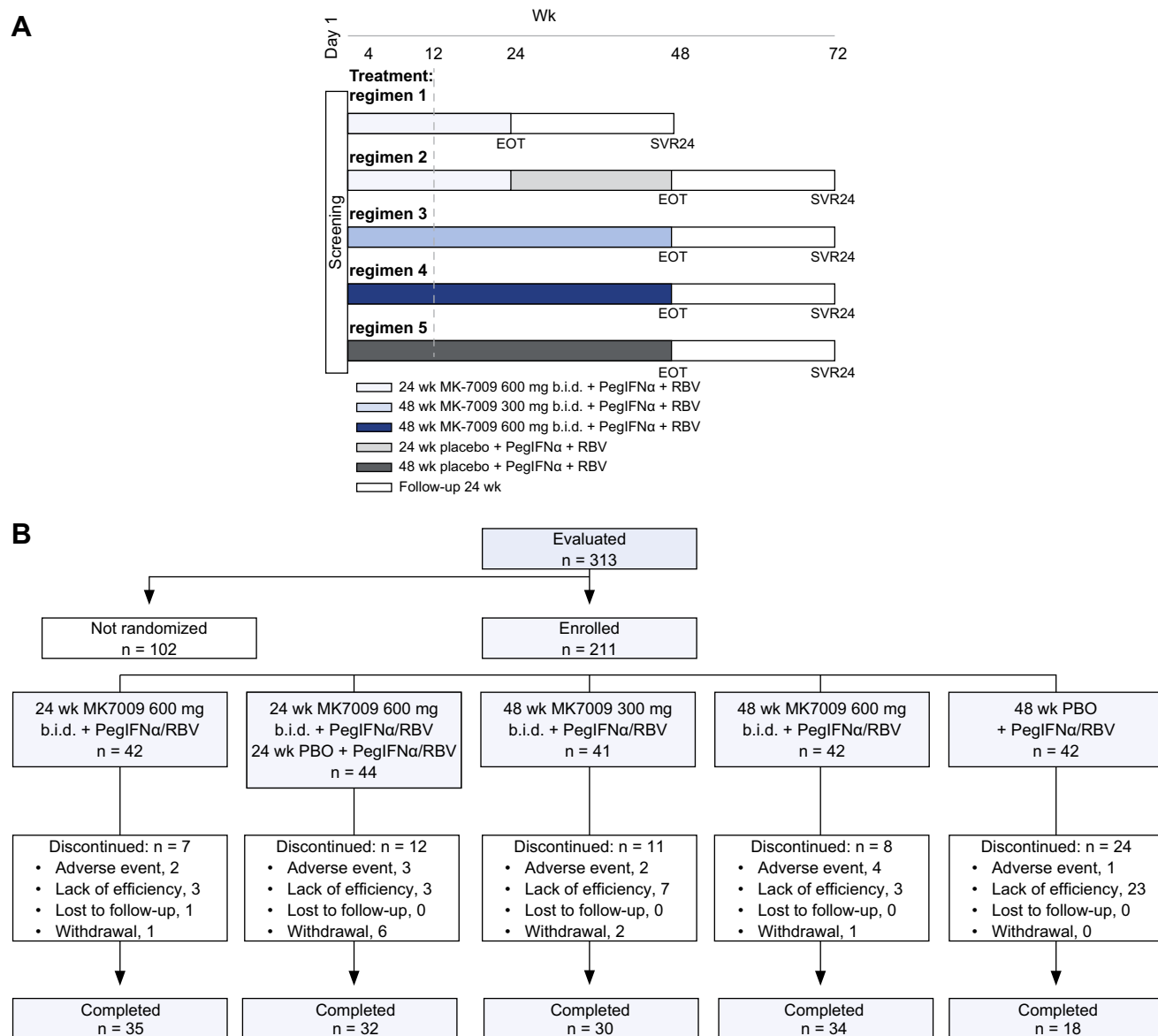

Fig. 1. **Study treatment overview**. (A) Study timeline, including the different treatment regimens. (B) CONSORT diagram detailing subject disposition with respect to study medication.

Table 1. Baseline patient characteristics.

| | 24 wk | | | | 48 wk | | | | | | Total | |
| | MK-7009 600 mg b.i.d + PegIFN + RBV | | MK-7009 600 mg b.i.d + PegIFN + RBV/24-wk PBO + PegIFN + RBV | | MK-7009 300 mg b.i.d + PegIFN + RBV | | MK-7009 600 mg b.i.d + PegIFN + RBV | | PBO + PegIFN + RBV | | | |
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	42		44		41		42		42		211	
Sex												
Male	22	(52.4)	27	(61.4)	29	(70.7)	27	(64.3)	26	(61.9)	131	(62.1)
Female	20	(47.6)	17	(38.6)	12	(29.3)	15	(35.7)	16	(38.1)	80	(37.9)
Age (yr)												
18 to 35	5	(11.9)	1	(2.3)	2	(4.9)	5	(11.9)	3	(7.1)	16	(7.6)
36 to 50	19	(45.2)	22	(50.0)	18	(43.9)	14	(33.3)	20	(47.6)	93	(44.1)
Over 50	18	(42.9)	21	(47.7)	21	(51.2)	23	(54.8)	19	(45.2)	102	(48.3)
Mean	48.2		50.5		49.9		50.4		49.1		49.6	
SD	8.9		8.1		7.9		9.1		8.4		8.5	
Median	49.0		50.0		51.0		51.0		49.0		50.0	
Range	29-64		32-64		28-65		23-65		28-64		23-65	
Race												
Asian	2	(4.8)	7	(15.9)	5	(12.2)	6	(14.3)	9	(21.4)	29	(13.7)
Black or African American	4	(9.5)	4	(9.1)	3	(7.3)	1	(2.4)	3	(7.1)	15	(7.1)
Multiracial	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	0	(0.0)	2	(0.9)
Native Hawaiian or other Pacific Islanders	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(0.5)
White	36	(85.7)	33	(75.0)	31	(75.6)	34	(81.0)	30	(71.4)	164	(77.7)
Ethnicity												
Hispanic or Latino	3	(7.1)	7	(15.9)	4	(9.8)	4	(9.5)	3	(7.1)	21	(10.0)
Not Hispanic or Latino	39	(92.9)	37	(84.1)	37	(90.2)	38	(90.5)	39	(92.9)	190	(90.0)
HCV genotype												
1a	18	(42.9)	17	(38.6)	17	(41.5)	21	(50.0)	15	(35.7)	88	(41.7)
1b	24	(57.1)	25	(56.8)	24	(58.5)	21	(50.0)	27	(64.3)	121	(57.3)
1 non-typeable	0	(0.0)	2	(4.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)
Hepatic fibrosis stage												
Metavir stage 0	5	(11.9)	3	(6.8)	0	(0.0)	4	(9.5)	0	(0.0)	12	(5.7)
Metavir stage 1	7	(16.7)	12	(27.3)	10	(24.4)	11	(26.2)	15	(35.7)	55	(26.1)
Metavir stage 2	11	(26.2)	13	(29.5)	10	(24.4)	7	(16.7)	13	(31.0)	54	(25.6)
Metavir stage 3	3	(7.1)	2	(4.5)	7	(17.1)	7	(16.7)	5	(11.9)	24	(11.4)
Stage by other methods	16	(38.1)	14	(31.8)	14	(34.1)	13	(31.0)	9	(21.4)	66	(31.4)
Prior treatment response												
Breakthrough	6	(14.3)	7	(15.9)	6	(14.6)	6	(14.3)	7	(16.7)	32	(15.2)
Null response	12	(28.6)	11	(25.0)	11	(26.8)	10	(23.8)	10	(23.8)	54	(25.6)
Partial response	8	(19.0)	8	(18.2)	8	(19.5)	9	(21.4)	9	(21.4)	42	(19.9)
Relapse	16	(38.1)	18	(40.9)	16	(39.0)	17	(40.5)	16	(38.1)	83	(39.3)
Screening HCV RNA												
<800,000 IU/ml	5	(11.9)	4	(9.1)	7	(17.1)	6	(14.3)	4	(9.5)	26	(12.3)
800,000 to <2,000,000 IU/ml	9	(21.4)	11	(25.0)	4	(9.8)	11	(26.2)	11	(26.2)	46	(21.8)
2,000,000 IU/ml to <5,000,000 IU/ml	15	(35.7)	9	(20.5)	12	(29.3)	7	(16.7)	11	(26.2)	54	(25.6)
5,000,000 to <10,000,000 IU/ml	6	(14.3)	7	(15.9)	7	(17.1)	14	(33.3)	4	(9.5)	38	(18.0)
≥10,000,000 IU/ml	7	(16.7)	13	(29.5)	11	(26.8)	4	(9.5)	12	(28.6)	47	(22.3)

MK-7009 was administered in combination with P/R in 4 regimens (one 300 mg b.i.d. regimen and three 600 mg b.i.d. regimens) to at least 40 patients per arm of the study (Fig. 1A). There was also a control arm that received placebo + P/R. Patients were stratified based on prior response to P/R (null response, partial response, breakthrough and relapse). Key inclusion criteria for entry into the study included chronic genotype (GT) 1 HCV-infected patients who have failed prior treatment(s) with P/R, a minimum of 25% of patients prior null responders, men and women 18–65 years of age, and baseline HCV RNA $\geqslant 4 \times 10^5$ IU/ml. Key exclusion criteria included non-HCV-related chronic hepatitis, HIV co-infection, evidence of cirrhosis on liver biopsy or approved non-invasive imaging, or any other condition contraindicated for treatment with P/R.

HCV RNA was measured at every scheduled study visit and detected by Roche Cobas Taqman. This assay has a lower limit of detection (LLoD) of 10 IU/ml and a lower limit of quantification (LLoQ) of 25 IU/ml.

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Table 2. SVR$_{24}$ rates in the ITT population.

Treatment	N	m	n (%)	Treatment *vs.* placebo + PegIFN + RBV at 24 week follow-up		
				Unadjusted difference in %	Adjusted difference in % (95% CI)*	*p* value
24-wk MK-7009 600 mg b.i.d + PegIFN + RBV	38	33	27 (71.1)	52.0	53.6 (34.5-69.1)	<0.001
24-wk MK-7009 600 mg b.i.d + PegIFN + RBV/24-wk PBO + PegIFN + RBV	38	32	32 (84.2)	65.2	64.4 (45.2-78.3)	<0.001
48-wk MK-7009 300 mg b.i.d + PegIFN + RBV	39	30	26 (66.7)	47.6	47.3 (29.2-63.2)	<0.001
48-wk MK-7009 600 mg b.i.d + PegIFN + RBV	41	34	32 (78.0)	59.0	59.0 (40.2-73.4)	<0.001
48-wk PBO + PegIFN + RBV	42	16	8 (19.0)			

*The adjusted difference is the difference of the two proportions (MK-7009 treatment regimen minus control regimen) adjusting for the stratification variable with Cochran Mantel-Haenszel (CMH) weights. The Miettinen and Nurminen method was used for this analysis.
N, number of patients included in the analysis; m, number of patients with an HCV RNA result at the 24 week follow-up visit; n (%) = number of patients with undetectable HCV RNA at the 24 week follow-up visit and the percentage calculated as (n/N) ∗ 100; CI, confidence interval; ITT, intention to treat.

Objectives

This study's primary safety objective was to evaluate the safety and tolerability of the MK-7009 300 mg b.i.d. treatment regimen and the three MK-7009 600 mg b.i.d. treatment regimens as compared with placebo in combination with 48 weeks of P/R (hereafter referred to as the control regimen), as assessed by review of the accumulated safety data.

The primary efficacy objective was to evaluate the antiviral activity of the three MK-7009 600 mg b.i.d. treatment regimens as compared with the control regimen, as assessed by the proportion of patients achieving undetectable HCV RNA 24 weeks after the end of all study therapy (sustained viral response 24 [SVR$_{24}$]).

Secondary objectives included: (1) to evaluate the antiviral activity of the MK-7009 300 mg b.i.d. treatment regimen as compared with the control regimen, as assessed by the proportion of patients achieving SVR$_{24}$; (2) to evaluate the antiviral activity of treatment regimen 1 (24 weeks of MK-7009 600 mg b.i.d. in combination with P/R) as assessed by the proportion of patients achieving SVR$_{24}$, as compared with response at treatment week 48 in the control regimen; (3) to evaluate the antiviral activity of MK-7009 300 mg b.i.d. treatment regimen and two MK-7009 600 mg b.i.d. treatment regimens (treatment regimens 2, 3, and 4) as compared with the control regimen, as assessed by the proportion of patients achieving undetectable viral RNA at treatment week 48.

Data analysis

Safety analyses are based on 'all patients as treated' (APaT) population. The full analysis set (FAS) population served as the primary population for the efficacy analysis. This population included all randomized patients who received at least one dose of study medication and had post-dose data. For this study, there is no difference in the results whether we use the FAS population or the Intent-to-Treat (ITT) population. Although we required the patients to have at least one post-randomization end point subsequent to at least one dose of study treatment to be included in the FAS population, every patient who was randomized and received at least one dose of study medication had at least one post-randomization HCV RNA measurement. Therefore, no patient was excluded based on the requirement of a post-randomization end point and the FAS population was identical to the ITT population.

With a sample size of ~40 per treatment arm, there was 82% power to demonstrate that at least one of the MK-7009 treatment regimens was superior to the control regimen as assessed by SVR$_{24}$. This assumes a true difference in SVR$_{24}$ of 32% at the point of maximum variability for a binary end point (for instance, SVR$_{24}$ of 66% for the MK-7009 treatment regimens and an SVR$_{24}$ of 34% for the control regimen; the maximum variability for a binary end point is 50%).

Criteria for virologic failure

HCV RNA data was provided to the designated unblinded Clinical Monitor and patients were discontinued from all study therapy if they met any of the following criteria for virologic failure: if the patient did not achieve at least a 2-log$_{10}$ IU/ml decline in HCV RNA from baseline by treatment week 12; if the patient had quantifiable HCV RNA at treatment week 24 (if the patient had positive but non-quantifiable HCV RNA at treatment week 24, a second measurement was taken at treatment week 28, if applicable; if the week 28 result was also positive,

the patient was discontinued from the study); if the patient had evidence of breakthrough viremia, as defined by: (1) a >1-log$_{10}$ increase from nadir viral RNA (nadir calculated from up to two consecutive HCV RNA measurements) in two consecutive visits by week 12, or (2) a plasma viral RNA of >100 IU/ml, in two consecutive visits after becoming undetectable; if the patient had evidence of relapse, as defined by two consecutive visits with detectable HCV RNA following the end of all study treatment after becoming undetectable on treatment.

Results

Overall, 211 patients were enrolled into the five treatment regimens (Fig. 1B). Of those, 62.1% were male (n = 131) and 37.9% were female (n = 80) (Table 1). Overall, 190 patients (90.0%) completed the study, and 20 (9.5%) discontinued (Supplementary Table 1). The most common reasons for study discontinuation were 'withdrawal by subject', and 'lost to follow-up'. The mean age of enrolled patients was 49.6 years, and age ranged from 23 to 65 years. Caucasian patients made up the majority of the population (77.7%), followed by Asian (13.7%) and Black/African American (7.1%) patients. The population was skewed slightly towards HCV 1b infection (57.3%); 41.7% of patients were infected with HCV 1a. Relapse made up the largest portion of prior failures (39.3%), followed by null response (25.6%), partial response (19.9%) and breakthrough (15.2%). Of the patients with *IL28B* SNP data available, 26 (19.8%) and 105 (80.2%) were CC and CT/TT, respectively.

SVR$_{24}$ rates in the ITT population can be seen in Table 2. Patients given 24 or 48 week courses of MK-7009 600 mg b.i.d. + P/R had SVR$_{24}$ rates of 71.1% and 78.0%, respectively. While there may be no obvious advantage to a longer treatment regimen, the study was not powered to discern differences between 24- and 48-week treatments. The SVR$_{24}$ rate in patients randomized to the 300 mg b.i.d. + P/R treatment regimen was 66.7%. The largest percentage of patients achieving SVR$_{24}$ (84.2%) was seen in the 24-wk 600 mg bid + P/R/24-wk PBO + P/R treatment group. SVR$_{24}$ in patients on MK-7009 + P/R was statistically superior to placebo + P/R in all treatment groups (*p* <0.001). Thirteen patients in the vaniprevir treatment groups were excluded from the primary analysis based on the pre-specified missing data approach. Patients who discontinued for administrative reasons, whose last HCV RNA measurement was undetectable prior to discontinuation, were not included. Patients who discontinued for treatment-related reasons, regardless of HCV RNA measurements, were considered failures. Reasons for virologic failure are listed in Supplementary Table 2.

Table 3. SVR$_{24}$ rates by (A) prior response to therapy and (B) genotype in the ITT population.

A		Breakthrough			Null response			Partial response			Relapse			Total		
		N		(%)	N		(%)	N		(%)	N		(%)	N		(%)
Patients included in the analysis		30		(15.1)	51		(25.8)	39		(19.6)	78		(39.2)	198		(100.0)
Treatment		N	m	n (% SVR$_{24}$)	N	m	n (% SVR$_{24}$)	N	m	n (% SVR$_{24}$)	N	m	n (% SVR$_{24}$)	N	m	n (% SVR$_{24}$)
24-wk MK-7009 600 mg b.i.d + PegIFN + RBV		5	3	2 (40.0)	12	10	6 (50.0)	7	6	6 (85.7)	14	14	13 (92.9)	38	33	27 (71.1)
24-wk MK-7009 600 mg b.i.d + PegIFN + RBV/24-wk PBO + PegIFN + RBV		7	6	6 (85.7)	9	7	7 (77.8)	6	5	5 (83.3)	16	14	14 (87.5)	38	32	32 (84.2)
48-wk MK-7009 300 mg b.i.d + PegIFN + RBV		5	4	3 (60.0)	10	5	4 (40.0)	8	5	3 (37.5)	16	16	16 (100.0)	39	30	26 (66.7)
48-wk MK-7009 600 mg b.i.d + PegIFN + RBV		6	5	4 (66.7)	10	6	5 (50.0)	9	9	9 (100.0)	16	14	14 (87.5)	41	34	32 (78.0)
48-wk PBO + PegIFN + RBV		7	3	2 (28.6)	10	1	0 (0.0)	9	3	1 (11.1)	16	9	5 (31.3)	42	16	8 (19.0)

| B		1a			1b			1 non-typeable			Total		
		N		(%)	N		(%)	N		(%)	N		(%)
Patients included in the analysis		81		(40.9)	115		(58.1)	2		(1.0)	198		(100.0)
Treatment		N	m	n (% SVR$_{24}$)	N	m	n (% SVR$_{24}$)	N	m	n (% SVR$_{24}$)	N	m	n (% SVR$_{24}$)
24-wk MK-7009 600 mg b.i.d + PegIFN + RBV		16	14	9 (56.3)	22	19	18 (81.8)	0	0	0 ( )	38	33	27 (71.1)
24-wk MK-7009 600 mg b.i.d + PegIFN + RBV/24-wk PBO + PegIFN + RBV		12	10	10 (83.3)	24	20	20 (83.3)	2	2	2 (100.0)	38	32	32 (84.2)
48-wk MK-7009 300 mg b.i.d + PegIFN + RBV		17	14	11 (64.7)	22	16	15 (68.2)	0	0	0 ( )	39	30	26 (66.7)
48-wk MK-7009 600 mg b.i.d + PegIFN + RBV		21	16	15 (71.4)	20	18	17 (85.0)	0	0	0 ( )	41	34	32 (78.0)
48-wk PBO + PegIFN + RBV		15	8	3 (20.0)	27	8	5 (18.5)	0	0	0 ( )	42	16	8 (19.0)

(A) N, number of patients included in the analysis by prior treatment response; (%), percentage of patients included in the analysis calculated as (prior treatment response N/total N) ∗ 100; m, number of patients with an HCV RNA result at the 24 week follow-up visit; n (% SVR$_{24}$), number of patients with undetectable HCV RNA at the 24 week follow-up visit and the percentage calculated as (n/N) ∗ 100.

(B) N, number of patients included in the analysis by HCV genotype; (%), percentage of patients included in the analysis calculated as (HCV genotype N/total N) ∗ 100; m, number of patients with an HCV RNA result at the 24 week follow-up visit; n (% SVR$_{24}$), number of patients with undetectable HCV RNA at the 24 week follow-up visit and the percentage calculated as (n/N) ∗ 100.

SVR$_{24}$ rates by prior response to therapy reveal that the highest response rates were seen in patients who previously either partially responded or relapsed (Table 3A). Importantly, the results of this analysis are based on small numbers due to the stratification into several patient groups. When SVR$_{24}$ rates were examined by HCV genotype, there were no obvious differences in response to two of the three MK-7009 treatment regimens between genotype 1a and 1b (Table 3B). Though the numbers are small, a difference that is evident between genotype 1a and genotype 1b is the response in patients given 24 weeks of treatment with MK-7009 600 mg b.i.d. SVR$_{24}$ in this population was 56.3% in patients with type 1a and 81.8% in patients with type 1b. However, no conclusive statements can be made as the study was not powered to study genotype subtype differences. Similarly, the samples sizes become small as the SVR rates are examined by baseline HCV RNA levels and fibrosis staging; thus the data were not instructive (data not shown).

IL28B status was collected from 131 patients who provided genetic consent and were analyzed in the per-protocol analyses. Of these, 19.8% (26/131) were CC, 59.5% were CT (78/131) and 20.6% were TT (27/131) for the SNP rs12979860. While IL28 genotype interactions were seen with SVR$_{24}$ when considering all treatment groups, the effect of IL28 genotype became non-significant when considering only the MK-7009 groups (data not

shown). Therefore it appears that the interaction was mainly driven by the difference in actual SVR$_{24}$ rates between PBO and MK-7009 treatment arms. Moreover, it was found that for each
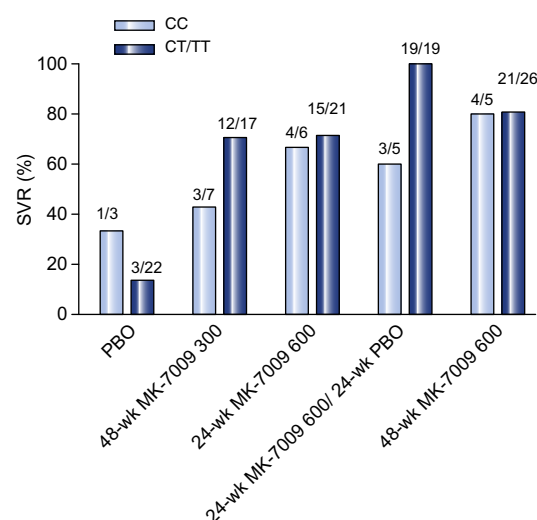
Fig. 2. Sustained viral response by IL28B (rs12979860) genotype.

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Table 4. Adverse events of clinical interest during the treatment phase.

	24 wk				48 wk					
	MK-7009 600 mg b.i.d + PegIFN + RBV		MK-7009 600 mg b.i.d + PegIFN + RBV/24-wk PBO + PegIFN + RBV		MK-7009 300 mg b.i.d + PegIFN + RBV		MK-7009 600 mg b.i.d + PegIFN + RBV		PBO + PegIFN + RBV	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	40		42		41		46		42	
With one or more drug-related adverse events	36	(90.0)	41	(97.6)	40	(97.6)	45	(97.8)	35	(83.3)
Blood and lymphatic system disorders	10	(25.0)	12	(28.6)	12	(29.3)	11	(23.9)	8	(19.0)
Anaemia	5	(12.5)	8	(19.0)	8	(19.5)	5	(10.9)	7	(16.7)
Leukopenia	2	(5.0)	2	(4.8)	0	(0.0)	1	(2.2)	0	(0.0)
Neutropenia	8	(20.0)	5	(11.9)	3	(7.3)	7	(15.2)	2	(4.8)
Thrombocytopenia	1	(2.5)	0	(0.0)	1	(2.4)	1	(2.2)	1	(2.4)
Gastrointestinal disorders	32	(80.0)	35	(83.3)	31	(75.6)	40	(87.0)	23	(54.8)
Diarrhea	17	(42.5)	18	(42.9)	13	(31.7)	25	(54.3)	5	(11.9)
Nausea	20	(50.0)	16	(38.1)	13	(31.7)	28	(60.9)	6	(14.3)
Vomiting	12	(30.0)	12	(28.6)	5	(12.2)	13	(28.3)	1	(2.4)
Skin and subcutaneous tissue disorders	23	(57.5)	26	(61.9)	26	(63.4)	32	(69.6)	19	(45.2)
Pruritus	14	(35.0)	13	(31.0)	12	(29.3)	14	(30.4)	8	(19.0)
Rash	6	(15.0)	6	(14.3)	6	(14.6)	14	(30.4)	7	(16.7)

Every patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MK-7009 treatment arm, there was no significant evidence that CC genotype patients achieved SVR$_{24}$ at a higher rate (Fig. 2).

In total, 83.3% of patients in the PBO arm and between 90.0% and 97.8% of patients in the MK-7009 treatment arms reported one or more drug-related adverse events during the treatment period (Table 4). Overall, between 5 and 8 patients in each of the MK-7009 treatment arms and 7 patients in the PBO arm had reported anemia. To address the anemia, 11 patients received epoetin beta during the trial. There were no significant differences in rates of anemia and rash between the MK-7009 regimens and the control group. No serious rashes were reported. Patients in MK-7009 regimens had higher rates of gastrointestinal adverse events as compared to control (Table 4). A complete adverse event summary is reported in Supplementary Table 3. The most common gastrointestinal adverse events reported were diarrhea, nausea, and vomiting. Most gastrointestinal adverse experiences were mild to moderate in intensity; few were severe (Supplementary Table 4). Other adverse events with incidences ⩾25% are shown in Supplementary Table 5.

Discussion

First generation HCV protease inhibitors such as boceprevir and telaprevir have strong antiviral efficacy, but need to be dosed frequently (8 or 12 h) and can be associated with anemia, dysgeusia, and skin rashes [21,22]. MK-7009 is a macrocyclic HCV NS3/4A protease inhibitor (administered QD or BID) that has demonstrated strong antiviral potency and a good safety profile in phase I studies [23].

In this report, MK-7009 (when combined with pegylated interferon alfa 2a and ribavirin) produced a significant improvement in the rate of SVR compared to retreatment with P/R in patients who had failed previous therapy for chronic hepatitis C. The highest rates of SVR$_{24}$ were seen in patients who relapsed after initial P/R treatment; where cumulatively MK-7009 treated patients had an SVR$_{24}$ of 94%. This result may be in part the result of the higher number of patients with genotype 1b, although the overall results appear to demonstrate no significant difference. The outcomes of this trial compare favorably to the trials of telaprevir and boceprevir [24,25]. In this trial, prior null responder patients had numerically higher SVR point estimates compared to the data from telaprevir- and boceprevir-based therapies, although direct comparisons of these data to previous data for boceprevir and telaprevir are precluded due to lack of head-to-head studies. Observed MK-7009 SVR$_{24}$ rates are similar to another 'first generation second wave' HCV protease inhibitor, TMC-435 [26]. Cirrhotic patients were randomized in this study in a separate cohort in a sequential fashion; the results will be analyzed once all cirrhotic patients have completed the follow-up visits.

Resistance is an important consideration in the use of HCV protease inhibitors [27]. Resistance-associated amino acid variants (RAVs) in response to MK-7009 therapy were predominantly observed at positions R155, A156 and/or D168 in non-SVR patients. This resistance profile is similar to other first generation NS3/4 inhibitors [28–31].

MK-7009 therapy at 300 mg and 600 mg b.i.d. was generally well tolerated for up to 48 weeks of therapy. Patients receiving MK-7009 regimens had higher rates of gastrointestinal (GI) adverse events (AEs) when compared with control. Most GI AEs were mild to moderate in severity. There were no significant differences in rates of anemia and rash between the patients receiving MK-7009 and control.

In conclusion, patients treated with MK-7009 plus P/R experienced significant improvement in SVR compared to P/R control in a population of GT 1 experienced patients. Results show that MK-7009 compares favorably with other first generation protease inhibitors. MK-7009 was generally well tolerated and most adverse experiences were mild to moderate in severity. Based

on these findings, the development of MK-7009 has advanced to phase 3 in Japan.

Conflict of interest

EL has received grants and/or consulting honoraria from Abbott, Achillon, Anadys, Biolex, Bristol-Myers Squibb, Boehringer Ingelheim, BioCryst, Biotica, Enanta, Gilead, GlaxoSmithKline, Globel-Immune, Idenix, Idera, Inhibitex, Intercept, Janssen, Medarex, Medtronic, Novartis, Merck, Sharp & Dohme Corp., Pharmasset, Presidio, Roche, Santaris, Scynexis, Tibotec, Theravance, Vertex, ViroChem Pharma and ZymoGenetics. EJG is a member of advisory boards with Roche, Gilead, Novartis and Abbott. SB, RJB, DA, JG, PH and NM are employees of Merck, Sharp & Dohme Corp., and may own stock and/or stock options.

References

[1] Liang TJ, Heller T. Pathogenesis of hepatitis C-associated hepatocellular carcinoma. Gastroenterology 2004;127:S62–S71.
[2] Manns MP, Foster GR, Rockstroh JK, Zeuzem S, Zoulim F, Houghton M. The way forward in HCV treatment – finding the right path. Nat Rev Drug Discov 2007;6:991–1000.
[3] Reesink HW, Zeuzem S, Weegink CJ, Forestier N, van Vliet A, Van de Wetering de Rooij J, et al. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase Ib, placebo-controlled, randomized study. Gastroenterology 2006;131:997–1002.
[4] Tsantrizos YS. Peptidomimetic therapeutic agents targeting the protease enzyme of the human immunodeficiency virus and hepatitis C virus. Acc Chem Res 2008;41:1252–1263.
[5] Jensen DM. A new era of hepatitis C therapy begins. N Engl J Med 2011;364:1272–1274.
[6] Kneteman NM, Howe AY, Gao T, Lewis J, Pevear D, Lund G, et al. HCV796: a selective nonstructural protein 5B polymerase inhibitor with potent anti-hepatitis C virus activity in vitro, in mice with chimeric human livers, and in humans infected with hepatitis C virus. Hepatology 2009;49:745–752.
[7] Koch U, Narjes F. Recent progress in the development of inhibitors of the hepatitis C virus RNA-dependent RNA polymerase. Curr Top Med Chem 2007;7:1302–1329.
[8] Pockros PJ, Nelson D, Godofsky E, Rodriguez-Torres M, Everson GT, Fried MW, et al. R1626 plus peginterferon Alfa-2a provides potent suppression of hepatitis C virus RNA and significant antiviral synergy in combination with ribavirin. Hepatology 2008;48:385–397.
[9] Wyles DL, Kaihara KA, Schooley RT. Synergy of a hepatitis C virus (HCV) NS4A antagonist in combination with HCV protease and polymerase inhibitors. Antimicrob Agents Chemother 2008;52:1862–1864.
[10] Lee C. Discovery of hepatitis C virus NS5A inhibitors as a new class of anti-HCV therapy. Arch Pharm Res 2011;34:1403–1407.
[11] Naggie S, Patel K, McHutchison J. Hepatitis C virus directly acting antivirals: current developments with NS3/4A HCV serine protease inhibitors. J Antimicrob Chemother 2010;65:2063–2069.
[12] Hadziyannis SJ, Sette Jr H, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–355.
[13] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–965.
[14] McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C immune. N Engl J Med 2009;361:580–593.
[15] Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet 2010;376:705–716.
[16] Sarrazin C, Rouzier R, Wagner F, Forestier N, Larrey D, Gupta SK, et al. SCH 503034, a novel hepatitis C virus protease inhibitor, plus pegylated interferon alpha-2b for genotype 1 nonresponders. Gastroenterology 2007;132:1270–1278.
[17] McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010;362:1292–1303.
[18] McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009;360:1827–1838.
[19] Shiffman ML, Esteban R. Triple therapy for HCV genotype 1 infection: telaprevir or boceprevir? Liver Int 2012;32:54–60.
[20] Manns MP, Gane E, Rodriguez-Torres M, Stoehr A, Yeh CT, Marcellin P, et al. Vaniprevir with peginterferon alfa-2a and ribavirin in treatment-naive patients with chronic hepatitis C - a randomized phase 2 study. Hepatology 2012;56(3):884–893.
[21] Poordad F, Bacon B, Bruno S, Mann M, Sulkowski M, Jacobson I, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195–1206.
[22] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales Jr FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–982.
[23] Liverton NJ, Carroll SS, Dimuzio J, Fandozzi C, Graham DJ, Hazuda D, et al. MK-7009, a potent and selective inhibitor of hepatitis C virus NS3/4A protease. Antimicrob Agents Chemother 2010;54:305–311.
[24] Bacon B, Gordon S, Lawitz E, Marcellin P, Vierling J, Zeuzem S, et al. Boceprevir for previously treated chronic HCVgenotype 1 infection. N Engl J Med 2011;364:1207–1217.
[25] Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417–2428.
[26] Tanwar S, Trembling PM, Dusheiko GM. TMC435 for the treatment of chronic hepatitis C. Expert Opin Investig Drugs 2012;21:1193–1209.
[27] Halfon P, Locarnini S. Hepatitis C virus resistance to protease inhibitors. J Hepatol 2011;55:192–206.
[28] Lenz O, Verbinnen T, Lin TI, Vijgen L, Cummings MD, Lindberg J, et al. In vitro resistance profile of the hepatitis C virus NS3/4A protease inhibitor TMC435. Antimicrob Agents Chemother 2010;54:1878–1887.
[29] Curry S, Qiu P, Tong X. Analysis of HCV resistance mutations during combination therapy with protease inhibitor boceprevir and PEGIFN alpha-2b using TaqMan mismatch amplification mutation assay. J Virol Methods 2008;153:156–162.
[30] Susser S, Welsch C, Wang Y, Zettler M, Domingues FS, Karey U, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology 2009;50:1709–1718.
[31] Tong X, Bogen S, Chase R, Girijavallabhan V, Guo Z, Njoroge FG, et al. Characterization of resistance mutations against HCV ketoamide protease inhibitors. Antiviral Res 2008;77:177–185.