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Vaniprevir With Pegylated Interferon Alpha-2a and Ribavirin in Treatment-Naïve Patients With Chronic Hepatitis C: A Randomized Phase II Study

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Vaniprevir (MK-7009) is a macrocyclic hepatitis C virus (HCV) nonstructural protein 3/4A protease inhibitor. The aim of the present phase II study was to examine virologic response rates with vaniprevir in combination with pegylated interferon alpha-2a (Peg-IFN-α-2a) plus ribavirin (RBV). In this double-blind, placebo-controlled, dose-ranging study, treatment-naïve patients with HCV genotype 1 infection (n = 94) were randomized to receive open-label Peg-IFN-α-2a (180 μg/week) and RBV (1,000-1,200 mg/day) in combination with blinded placebo or vaniprevir (300 mg twice-daily [BID], 600 mg BID, 600 mg once-daily [QD], or 800 mg QD) for 28 days, then open-label Peg-IFN-α-2a and RBV for an additional 44 weeks. The primary efficacy endpoint was rapid viral response (RVR), defined as undetectable plasma HCV RNA at week 4. Across all doses, vaniprevir was associated with a rapid two-phase decline in viral load, with HCV RNA levels approximately $3\log_{10}$ IU/mL lower in vaniprevir-treated patients, compared to placebo recipients. Rates of RVR were significantly higher in each of the vaniprevir dose groups, compared to the control regimen (68.8%-83.3% versus 5.6%; $P < 0.001$ for all comparisons). There were numerically higher, but not statistically significant, early and sustained virologic response rates with vaniprevir, as compared to placebo. Resistance profile was predictable, with variants at R155 and D168 detected in a small number of patients. No relationship between interleukin-28B genotype and treatment outcomes was demonstrated in this study. The incidence of adverse events was generally comparable between vaniprevir and placebo recipients; however, vomiting appeared to be more common at higher vaniprevir doses. *Conclusion*: Vaniprevir is a potent HCV protease inhibitor with a predictable resistance profile and favorable safety profile that is suitable for QD or BID administration.
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Since 2001, the combination of pegylated interferon alpha (Peg-IFN-α) plus ribavirin (RBV) has been the standard-of-care treatment for patients with hepatitis C virus (HCV) infection.[1-3] However, the recent approval of two novel HCV nonstructural protein (NS)3/4A protease inhibitors (boceprevir and telaprevir) heralds a new era in the treatment of chronic hepatitis C.[4-8] For treatment-naïve patients, the addition of these agents to a Peg-IFN plus RBV backbone increases rates of sustained virologic response (SVR) from 40%-50% to approximately 70%.[4,6] In addition, triple therapy with HCV protease inhibitors can be truncated to 24 or 28 weeks in 50%-60% of treatment-naïve patients who clear the virus early on treatment.[9] However, these first-

Abbreviations: AEs, adverse events; APaT, all-patients-as-treated population; AUC, area under the plasma-concentration versus time curve; BID, twice-daily; bp, base pair; C_{24h}, concentration of drug in the plasma at 24 hours after dose; CI, confidence interval; C_{max}, maximum concentration; C_{trough}, trough concentration of drug in the plasma; ECGs, electrocardiographs; EVR, early viral response; HCV, hepatitis C virus; IL, interleukin; LOD, limit of detection; LOQ, lower limit of quantification; NS, nonstructural protein; PCR, polymerase chain reaction; Peg-IFN-α-2a, pegylated interferon alpha-2a; PK, pharmacokinetic; PP, per protocol; QD, once-daily; RAVs, resistance-associated amino-acid variants; RBV, ribavirin; RVR, rapid viral response; SVR, sustained virologic response; T_{max}, time to maximum plasma concentration.

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generation HCV protease inhibitors have to be administered three times per day with fatty meals and also have additional side effects, including anemia, rash, dysgeusia, and gastrointestinal symptoms. Therefore, new HCV protease inhibitors are needed with more favorable pharmacokinetic, safety, and tolerability profiles.

The HCV NS3/4A protease is one of the most promising drug targets for hepatitis C therapeutics.[10] NS3/4A HCV protease inhibitors achieve high antiviral potency by blocking HCV polyprotein cleavage and may also neutralize HCV NS3 protease-mediated interference with the innate immune system. Through this mechanism, HCV NS3/4A protease inhibitors reverse the HCV NS3 protein's capacity to block intracellular signal-transduction pathways for endogenous IFN production *in vitro* and may also do so *in vivo*.[11,12] Several linear and macrocyclic so-called second-wave HCV protease inhibitors with twice-daily (BID) or once-daily (QD) dosing are currently in the early stages of clinical development, including BILN 201335,[13] TMC 435,[14,15] and ITMN 191.[16]

Vaniprevir (MK-7009) is a macrocyclic second-wave HCV NS3/4A protease inhibitor with QD or BID dosing that has demonstrated potent antiviral efficacy and good tolerability in a 14-day phase I monotherapy trial.[17,18] In the present phase II study, we examined rapid virologic response (RVR), early virologic response (EVR), and SVR rates with vaniprevir in combination with Peg-IFN-α-2a plus RBV when administered for 28 days, followed by Peg-IFN-α-2a plus RBV alone for an additional 44 weeks.

Patients and Methods

Study Design and Patient Population. This was a double-blind, randomized, placebo-controlled, dose-ranging, multicenter study to evaluate the safety and efficacy of vaniprevir. The study was conducted in accord with principles of good clinical practice and was approved by the appropriate institutional review boards and regulatory agencies. Patient safety was overseen by an external data-monitoring committee, and informed consent was documented for each patient before study enrollment.

Adult, treatment-naïve patients with chronic, compensated, HCV genotype 1 infection, defined as HCV RNA levels $\geq 4 \times 10^5$ IU/mL at screening (i.e., within 75 days preceding the first dose of vaniprevir or placebo), were enrolled. All patients had positive serology for HCV or detectable HCV RNA $\geq$6 months before study initiation. Patients with evidence of cirrhosis by histology, imaging, or physical findings were excluded.

Patients were randomly assigned to one of five treatment groups in a 1:1:1:1:1 ratio using a central randomization procedure by an interactive voice response system. Patients received matching-image placebo or vaniprevir at a dose of 300 mg BID, 600 mg BID, 600 mg QD, or 800 mg QD. Treatment with vaniprevir or placebo was blinded and administered concomitantly with open-label Peg-IFN-α-2a (Pegasys; Roche, Nutley, NJ) and RBV (Copegus; Roche) 180 μg/week + 1,000-1,200 mg/day for 28 days. Thereafter, all patients continued on open-label treatment with Peg-IFN-α-2a and RBV according to the local product label (typically for an additional 44 weeks).

Pharmacokinetic Measurements. All patients participated in either a sparse population-pharmacokinetic (PK) cohort or in an optional intensive-PK cohort, which involved a more intensive schedule of sample collection. Patients who participated in the population-PK cohort were stratified based on HCV genotype (i.e., 1a versus other genotype 1 subtypes). Plasma

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Potential conflict of interest: Dr. Manns is on the speakers' bureau of, and serves as a consultant to Roche, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, and Merck; serves as consultant to Boehringer-Ingelheim, Novartis, Tibotec, and Vertex; he has received grant/research support from Roche, Gilead, Novartis, Boehringer-Ingelheim, Bristol-Myers Squibb, and Merck. Dr. Gane has served as an advisor to Novartis, Janssen Cilag, and Gilead. Dr. Rodriguez-Torres consults for Hoffmann- La Roche, Abbott Laboratories, Pharmasset, Akros, Genentech, Bristol-Myers Squibb, Novartis, Merck, Inhibitex, Santaris, and GlaxoSmithKline and has received grant/research support from Vertex, Anadys, Hoffman La Roche, Genentech, GlaxoSmithKline, Novartis, Bristol-Myers Squibb, Vertex Pharmaceuticals, Idera, Pharmasset, Sanofi-Aventis, Merck, Abbott Laboratories, Pfizer, Human Genome Sciences, Gilead, Johnson & Johnson, Zymogenetics, Akros, Scynexis, Santaris, Mochida, Boehringer-Ingelheim, Inhibitex, Idenix, and Siemens. Dr. Stoehr is on the speakers' bureau of Merck and Roche. Dr. Yeh has nothing to disclose. Dr. Marcellin has received grants from and served as investigator, speaker, and expert for Roche, Gilead, Janssen-Tibotec, and Merck; he has served as investigator, speaker, and expert for Bristol-Myers Squibb, Novartis, and Pharmasset; has served as investigator and expert for Vertex and Abbott; has served as an investigator for Boehringer-Ingelheim and Pfizer; and received grants and served as an investigator for Echosens. Drs. Wiedmann, Hwang, Caro, and Lee are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ. Dr. Barnard is an employee of and owns stock in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ.

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concentrations of vaniprevir were determined using liquid-liquid extraction, followed by high-performance liquid chromatography/tandem mass spectrometry analysis. The lower limit of quantitation (LOQ) for the plasma assay was 1 ng/mL (1.32 nM) and the linear calibration range was 1-1,000 ng/mL.

Sparse population PK samples were collected on selected days up to week 72. In addition, samples were also collected at multiple time points over the 12- or 24-hour dosing period for the subset of patients (~4-8 patients per treatment group) included in the intensive-PK cohort. For all patients, the concentration of drug in the plasma at 2 hours after dose and the trough concentration of drug in the plasma (C_{trough}: concentration of drug in the plasma at 12 hours after dose for BID regimens and concentration of drug in the plasma at 24 hours after dose [C_{24h}] for QD regimens) were assessed. The following additional plasma PK parameters were assessed for the intensive-PK cohort: area under the plasma-concentration versus time curve ($AUC_{0\text{-}12h}$ for the BID regimens and $AUC_{0\text{-}24h}$ for the QD regimens), time to reach maximum concentration (C_{max}) (T_{max}), and accumulation ratio, as appropriate. The accumulation of vaniprevir was determined by calculating the ratio of the PK parameter value (i.e., AUC, C_{max}, and C_{trough}) on days 28 and 1. WinNonlin (Pharsight Corporation, Mountain View, CA) was used to determine PK parameters.

Endpoints. The primary efficacy endpoint was the proportion of patients achieving RVR, defined as plasma HCV RNA below the limit of detection (LOD) at week 4. Exploratory efficacy endpoints included the proportion of patients achieving EVR (defined as plasma HCV RNA below the LOD at week 12) and the proportion of patients achieving SVR (defined as plasma HCV RNA below the LOD 24 weeks after completing treatment with Peg-IFN and RBV). The per-protocol (PP) population was predefined as the primary efficacy-analysis population. This excluded patients who had important deviations from the protocol, such as those taking prohibited medications or who fell below predetermined levels of compliance required for each component of the treatment. Only patients with HCV RNA results at week 4 were included in the analysis of RVR using the predefined missing primary data approach of data as observed (i.e., missing data were not replaced). For the analysis of SVR, patients with missing data during the 24-week follow-up period were considered as treatment failures, using an expanded missing data approach.

Plasma HCV RNA levels were assessed using a commercially available reverse-transcriptase polymerase chain reaction (PCR) assay (Roche COBAS TaqMan HCV/HPS assay, v2.0). The linear range of the assay is from 25 IU/mL (LOQ) to 391,000,000 IU/mL of HCV RNA (upper LOQ). The lower LOD of the assay is 10 IU/mL. Baseline HCV RNA was defined as the mean of two HCV RNA values: one measured 2-7 days before dosing and the other measured on the first day of dosing. If one of these HCV RNA values was missing, the single available value was used.

The tolerability of vaniprevir was monitored from the first study dose through to 14 days after the last study dose (i.e., day 42) by the clinical evaluation of adverse events (AEs) reported by the patient and by repeated measurements of vital signs (e.g., heart rate, blood pressure, respiration rate, and oral temperature), 12-lead electrocardiographs (ECGs), physical examinations, body weight, and standard laboratory safety tests (i.e., blood chemistry, hematology, and urinalysis).

HCV Resistance Measurements. The presence of resistance-associated amino-acid variants (RAVs) was assessed during the first 42 days of dosing using a population resistance-sequencing assay with a detection limit of 1,000 IU/mL for both genotypes 1a and 1b. Baseline samples were selected for resistance analysis from all patients and from selected patients during treatment who exhibited viral breakthrough or who were nonresponsive to treatment during the first 42 days of dosing, as defined by the clinical protocol. Viral breakthrough was defined as a $>1\log_{10}$ increase from nadir HCV RNA at two consecutive HCV RNA measurements or plasma HCV RNA >100 IU/mL in two consecutive visits after becoming undetectable. A nonresponder was defined as a patient who experienced a $\leq 2\log_{10}$ decrease in HCV RNA levels through day 28.

Population sequences were aligned to either H77 (GenBank NC_004102) or Con1 (GenBank AJ238799) for genotypes 1a and 1b, respectively. For resistance analysis, eight independent PCR reactions were attempted for each sample. Depending on the number of amplicons obtained, a maximum of four of these products were directly sequenced per time point (i.e., population sequencing).

Interleukin-28B *Analysis.* To determine host genetic determinants of response to Peg-IFN-α-2a/RBV or MK-7009 therapy, informed consent and blood samples for interleukin (*IL*)*28B* genetic analysis were requested from all study participants. Blood samples for genetic analysis were collected in an ethylene diamine tetraacetic acid tube at the study site. Samples were centrifuged, plasma was discarded, and cell pellets were stored frozen until DNA extraction and

genotyping analysis. Subject samples were genotyped for *IL28B* rs12979860, rs12980275, and rs8103142 alleles at an outsourced vendor using vendor-proprietary DNA Sanger sequencing assays.

Statistical Analysis. This study was designed to randomize a total of 85 patients into five treatment groups. With evaluable data expected from approximately 75 patients (15 patients per treatment group), response rates of 75% in the vaniprevir/Peg-IFN-α-2a/RBV group and 20% in the placebo/Peg-IFN-α-2a/RBV group at week 4 would result in 90% power to declare the treatment with vaniprevir as superior to placebo. The PP population was predefined as the primary analysis population for the analysis of RVR, and data as observed was predefined as the missing data approach. The full analysis set population included all randomized patients who received at least one dose of study medication and had at least one postdose endpoint data: This population was used for the analysis of EVR and SVR endpoints. For these two endpoints, patients missing a measurement were considered to have failed treatment (i.e., expanded missing data approach). The all-patients-as-treated (APaT) population was used for the safety analyses. The APaT population consisted of all randomized patients who received at least one dose of study treatment. Moreover, patients were included in the treatment group corresponding to the study treatment they actually received.

The planned comparisons were between each vaniprevir/Peg-IFN-α-2a/RBV treatment group and the placebo/Peg-IFN-α-2a/RBV group. A closed testing procedure with a fixed sequence of tests was used to account for multiplicity within the BID and QD treatment arms, with the higher dose tested first and the lower dose tested only if the first was significant. This ensured strong control of error rates within the BID and QD arms, but not across all arms. To compare the rates of RVR between the vaniprevir and placebo groups, 95% confidence intervals (CIs) were calculated using Miettinen and Nurminen's method. Genotype (i.e., 1a versus all other subtypes of genotype 1) was used as a stratification variable in the analyses.

Results

Patient Population. In total, 94 patients were randomized, received at least one dose of study medication, and completed the 28-day triple-therapy dosing period (Fig. 1). Of these, 78 patients (88%) completed 48 weeks of therapy with Peg-IFN-α-2a and RBV, and 84 patients completed the 6-month post-therapy follow-up (6 patients who discontinued Peg-IFN-α-2a and RBV early were followed up 6 months after their last dose).

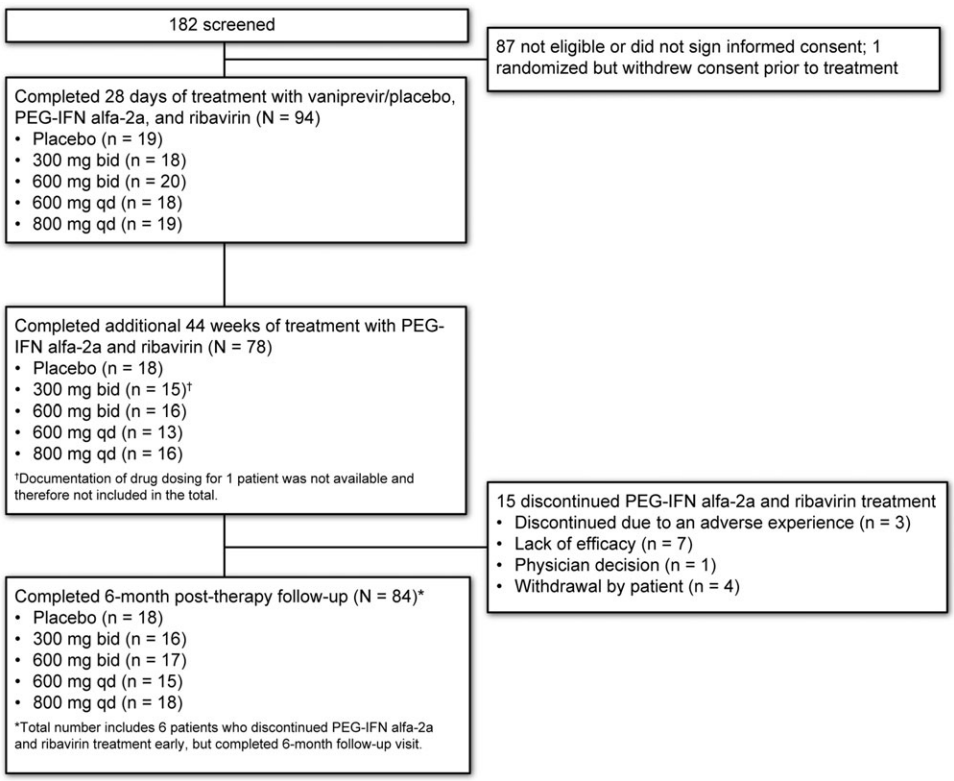

Fig. 1. Patient disposition.

Table 1. Patient Characteristics

Characteristics	Placebo + Peg-IFN-α-2a + RBV (n = 19)	Vaniprevir 300 mg BID + Peg-IFN-α-2a + RBV (n = 18)	Vaniprevir 600 mg BID + Peg-IFN-α-2a + RBV (n = 20)	Vaniprevir 600 mg QD + Peg-IFN-α-2a + RBV (n = 18)	Vaniprevir 800 mg QD + Peg-IFN-α-2a + RBV (n = 19)	Total (N = 94)
Gender, n (%)						
Male	11 (57.9)	14 (77.8)	11 (55.0)	7 (38.9)	12 (63.2)	55 (58.5)
Female	8 (42.1)	4 (22.2)	9 (45.0)	11 (61.1)	7 (36.8)	39 (41.5)
Age (years), n (%)						
18-35	2 (10.5)	3 (16.7)	6 (30.0)	1 (5.6)	4 (21.1)	16 (17.0)
36-50	9 (47.4)	8 (44.4)	10 (50.0)	8 (44.4)	7 (36.8)	42 (44.7)
>50	8 (42.1)	7 (38.9)	4 (20.0)	9 (50.0)	8 (42.1)	36 (38.3)
Mean (SD)	47.8 (10.1)	46.7 (10.2)	42.0 (10.7)	50.1 (8.4)	45.1 (12.0)	46.2 (10.5)
Median (range)	46.0 (32-66)	46.0 (27-65)	44.0 (22-58)	50.5 (34-65)	44.0 (21-65)	45.5 (21-66)
Race, n (%)						
Asian	2 (10.5)	1 (5.6)	1 (5.0)	2 (11.1)	2 (10.5)	8 (8.5)
Black or African American	2 (10.5)	2 (11.1)	3 (15.0)	2 (11.1)	1 (5.3)	10 (10.6)
Multiracial	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)
Native Hawaiian or other Pacific Islander	1 (5.3)	1 (5.6)	0 (0.0)	1 (5.6)	0 (0.0)	3 (3.2)
White	12 (63.2)	14 (77.8)	16 (80.0)	13 (72.2)	16 (84.2)	71 (75.5)
Ethnicity, n (%)						
Hispanic or Latino	3 (15.8)	3 (16.7)	4 (20.0)	3 (16.7)	4 (21.1)	17 (18.1)
Not Hispanic or Latino	16 (84.2)	15 (83.3)	16 (80.0)	15 (83.3)	15 (78.9)	77 (81.9)
HCV genotype,* n (%)						
1a	8 (42.1)	7 (38.9)	8 (40.0)	7 (38.9)	8 (42.1)	38 (40.4)
1b	9 (47.4)	8 (44.4)	9 (45.0)	8 (44.4)	7 (36.8)	41 (43.6)
1 not otherwise typeable	2 (10.5)	3 (16.7)	3 (15.0)	3 (16.7)	4 (21.1)	15 (16.0)

Abbreviation: SD, standard deviation.

*These genotype results were provided by the central laboratory. If resistance analyses were performed on any patient, the HCV genotype would also be reported with the resistance analyses and may differ from these results.

Patients were enrolled at 32 study centers across 13 countries. Approximately 75% of enrolled patients were white and 59% were male (Table 1), and distribution of patients with HCV genotypes 1a and 1b was generally well balanced across the dose groups. There were no clinically meaningful differences between treatment groups at baseline with respect to patient characteristics.

PK. Patient randomization was balanced across the five treatment groups, both within the intensive-PK cohort and within the two strata (i.e., genotype 1a versus other genotype 1 subtypes) of the population-PK cohort. Results from the intensive-PK cohort demonstrate that vaniprevir is rapidly absorbed, with a median plasma T_{max} of 1.5-3 hours at all dose levels. Vaniprevir exposure (i.e., $AUC_{0\text{-}12h}$ for BID doses and $AUC_{0\text{-}24h}$ for QD doses) at steady state was 5.15, 23.36, 17.77, and 14.76 $\mu M \cdot h$ for doses of 300 mg BID, 600 mg BID, 600 mg QD, and 800 mg QD, respectively. With BID dosing, there was some accumulation, with a geometric mean accumulation ratio of 1.2-1.8 for $AUC_{0\text{-}12h}$ and C_{max}.

Both $AUC_{0\text{-}12h}$ and C_{max} appeared to increase greater than dose proportionally between 300- and 600-mg BID doses. The intersubject variability for AUC, C_{max}, and C_{trough} was high (i.e., greater than 30% coefficient of variation) for each dosing regimen. With QD administration, there was extensive overlap in individual $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} values between 600- and 800-mg QD doses because of the high variability. Steady-state C_{trough} concentrations on day 28 after QD doses (25 μM for 600 mg QD and 30 μM for 800 mg QD) were similar and generally lower than the BID doses (65 μM for 300 mg BID and 100 μM for 600 mg BID). Trough concentrations after morning and evening doses for both BID dosing regimens were generally similar.

Efficacy. Figure 2 illustrates change in the mean $\log_{10}$ HCV RNA at day 1 through day 42, which includes 28 days of triple therapy followed by 14 days of Peg-IFN-α-2a and RBV alone. In all dose groups, vaniprevir was associated with a rapid two-phase decline in HCV RNA, compared to the more gradual decrease in viral load observed in patients receiving placebo. HCV RNA levels were approximately $3\log_{10}$ IU/mL lower in vaniprevir-treated patients, compared to placebo recipients, during the vaniprevir dosing period.

Rates of RVR were significantly higher in each of the vaniprevir dose groups, compared to the control regimen, satisfying the primary hypothesis that at least one vaniprevir dose group would result in higher RVR

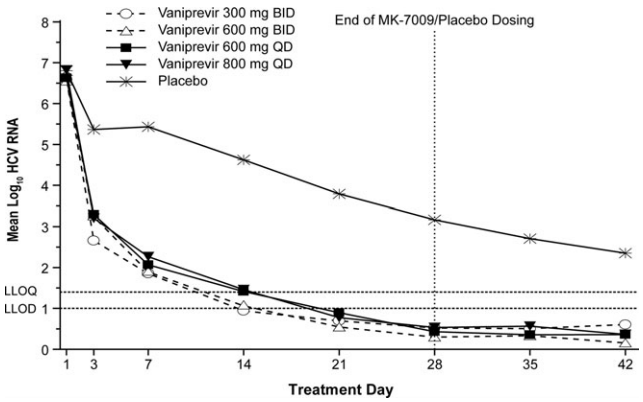

Fig. 2. Mean $\log_{10}$ HCV RNA. Plotted is the mean $\log_{10}$ HCV RNA at day 1 through day 42 for each of the five treatment groups. Vaniprevir was dosed for 28 days in combination with Peg-IFN-α-2a and RBV, which were continued for an additional 44 weeks. All doses were given in combination with Peg-IFN-α-2a and RBV. Dotted lines: lower limit of quantification (LLOQ) (25 copies/mL) and lower limit of detection (LLOD) (10 copies/mL) of the HCV RNA assay. Imputed values for samples with HCV RNA less than LLOQ and LLOD were 12.5 and 1, respectively.

rates than placebo (Table 2; PP analysis, N = 88). The full analysis set population (N = 94) showed nearly identical results (Supporting Table 1). Rates of RVR also appeared dose related among vaniprevir recipients, with numerically higher responses in patients receiving 600 mg BID and 800 mg QD compared with those receiving 300 mg BID and 600 mg QD (78.9% and 83.3% versus 75.0% and 68.8%); however, the study was not powered to perform formal statistical comparisons between vaniprevir dose groups.

All vaniprevir treatment regimens also had numerically higher EVR and SVR rates, compared to the control regimen (P = not significant; Table 3). However, the difference in rates of SVR between vaniprevir and placebo treatment groups did not achieve statistical significance, which was expected given the relatively small sample size and the focus of the study design on the RVR endpoint.

HCV Resistance. Baseline population resistance sequence data were available for 84 of the 94 patients in the study. One genotype 1b–infected patient (AN 3300) exhibited the D168E variant at baseline (Table 4). This patient showed a slow decline in HCV RNA throughout the 28-day vaniprevir dosing period (classified as a "slow responder"), although this patient did not meet the protocol-defined failure criteria (Fig. 3). Resistance analysis revealed that viruses harbored the D168E variant at baseline, before vaniprevir dosing, and throughout the vaniprevir dosing period (Table 4).

Of the 10 protocol-defined failures identified in the study, postbaseline resistance testing was not performed in 5 patients because of low HCV RNA levels (<1,000 IU/mL by day 42 of the study). Of the remaining 5 patients, 2 genotype 1b–infected patients (ANs 2957 and 3290) receiving placebo did not exhibit a greater than $2\log_{10}$ decrease in HCV RNA during the dosing period (classified as "nonresponders"). RAVs were not detected in viruses from these patients by population sequencing (Table 4). The R155K variant was detected in viruses from 1 genotype 1a–infected patient (AN 3249), who exhibited a greater than $1\log_{10}$ increase from nadir while receiving vaniprevir 800 mg QD (classified as a "breakthrough") (Fig. 3). Two patients (1 infected with genotype 1a and 1 with genotype 1b) who received vaniprevir 300 mg BID exhibited a greater than $1\log_{10}$ increase in HCV RNA from nadir after completion of the 28-day vaniprevir dosing period (classified as "relapse after vaniprevir/placebo dosing"). RAVs R155K and D168V were detected by population sequencing in the genotype 1a–infected patient (AN 3242; Table 4). Clonal analysis revealed that these RAVs were not linked (data on file; Merck & Co., Inc., Whitehouse Station, NJ). RAVs D168V and D168T were identified in viruses from the genotype 1b–infected patient (AN 2966).

Table 2. RVR Rates

				Treatment Versus Placebo + Peg-IFN-α-2a + RBV		
Treatment	N	m	RVR (n) (%)	Unadjusted Difference (%)	Adjusted Difference (%) (95% CI)*	*P* Value
RVR (week 4)						
Placebo + Peg-IFN-α-2a + RBV	18	18	1 (5.6)			
Vaniprevir 300 mg BID + Peg-IFN-α-2a + RBV	16	16	12 (75.0)	69.4	69.3 (40.3, 86.7)	<0.001
Vaniprevir 600 mg BID + Peg-IFN-α-2a + RBV	19	19	15 (78.9)	73.4	73.6 (46.0, 88.6)	<0.001
Vaniprevir 600 mg QD + Peg-IFN-α-2a + RBV	17	16	11 (68.8)	63.2	63.3 (32.8, 82.7)	<0.001
Vaniprevir 800 mg QD + Peg-IFN-α-2a + RBV	18	18	15 (83.3)	77.8	77.8 (49.2, 91.3)	<0.001

RVR analysis was based on the predefined PP population (N = 88).

Abbreviations: N, number of patients in the analysis population; m, number of patients in the analysis population with an HCV RNA result at the analysis time point; n (%), number of patients in the analysis population with undetectable HCV RNA at the analysis time point and the percentage calculated as (n/m)*100.

*Based on Miettinen and Nurminen's method with stratification by genotype (1a versus not 1a).

Table 3. EVR and SVR Rates

Treatment	N	m	Virologic Response (n) (%)	Treatment Versus Placebo + Peg-IFN-α-2a + RBV: Unadjusted Difference (%)	Treatment Versus Placebo + Peg-IFN-α-2a + RBV: Adjusted Difference (%) (95% CI)*
EVR (week 12)					
Placebo + Peg-IFN-α-2a + RBV	19	16	9 (47.4)		
Vaniprevir 300 mg BID + Peg-IFN-α-2a + RBV	18	17	14 (77.8)	30.4	30.3 (−1.8, 56.8)
Vaniprevir 600 mg BID + Peg-IFN-α-2a + RBV	20	19	17 (85.0)	37.6	37.5 (7.4, 62.0)
Vaniprevir 600 mg QD + Peg-IFN-α-2a + RBV	18	16	14 (77.8)	30.4	30.0 (−1.9, 56.5)
Vaniprevir 800 mg QD + Peg-IFN-α-2a + RBV	19	18	14 (73.7)	26.3	26.3 (−5.5, 53.5)
SVR (24-week follow-up)					
Placebo + Peg-IFN-α-2a + RBV	19	18	12 (63.2)		
Vaniprevir 300 mg BID + Peg-IFN-α-2a + RBV	18	16	11 (61.1)	−2.0	−2.5 (−33.1, 28.2)
Vaniprevir 600 mg BID + Peg-IFN-α-2a + RBV	20	17	16 (80.0)	16.8	17.0 (−12.2, 44.0)
Vaniprevir 600 mg QD + Peg-IFN-α-2a + RBV	18	15	14 (77.8)	14.6	14.4 (−16.1, 42.4)
Vaniprevir 800 mg QD + Peg-IFN-α-2a + RBV	19	18	16 (84.2)	21.1	21.1 (−8.0, 47.4)

EVR and SVR analyses were based on the full analysis set population with expanded missing data handling.

Abbreviations: N, number of patients in the analysis population; m, number of patients in the analysis population with an HCV RNA result at the analysis time point; n (%), number of patients in the analysis population with undetectable HCV RNA at the analysis time point and the percentage calculated as (n/N)*100.

*Based on Miettinen and Nurminen's method with stratification by genotype (1a versus not 1a).

IL28B *Genotyping.* In total, 70 patients provided consent for inclusion in the host genetic analysis, but 3 samples had insufficient template. The *IL28B* genotype analysis therefore compared genotype at loci rs12979860, rs12980275, and rs8103142 with RVR and SVR outcomes in 67 patients with samples available for testing from all treatment groups. *IL28B* genotype did not correlate significantly with SVR outcome (Supporting Table 3 and data not shown; $P = 0.486$ for rs12979860), in contrast to previous published work on response to Peg-IFN-α-2a/RBV treatment in a larger cohort of patients.[19] *IL28B* genotype also did not associate with the primary endpoint for this study, RVR (Supporting Table 4 and data not shown; $P = 0.312$ for rs12979860).

Safety. In total, AEs were reported by 85 (90.4%) of the 94 treated patients across all treatment groups, with no notable between-group differences (Table 5). Among patients receiving vaniprevir, nausea (34.7%), headache (33.3%), influenza-like illness (22.7%), and fatigue (21.3%) were the most frequently reported AEs. These incidence rates were generally comparable with those among patients in the placebo group: nausea (26.3%), headache (36.8%), influenza-like illness (21.1%), and fatigue (36.8%). However, vomiting was reported by 40.0% (8 of 20) of the patients in the vaniprevir 600-mg BID group, compared to 0% (0 of 19) of the patients in the placebo group, and the difference of 40.0% (95% CI: 19.9%-61.6%) was nominally statistically significant, as evidenced by the 95% CI excluding zero. In total, 14 patients receiving

Table 4. HCV-Resistant Variants Detected by Population Sequencing*

Patient Allocation No.	Vaniprevir Dose	Genotype 1 Subtype	Resistance Variants Identified at Baseline	Resistance Variants Identified at Week 4†
3242	300 mg BID	1a	ND	R155K/D168V
2966	300 mg BID	1b	ND	D168T/I/A/V
3249	800 mg QD	1a	ND	R155K
03300	800 mg QD	1b	D168E	D168E
02957	Placebo	1b	ND	ND
03290	Placebo	1b	ND	ND

Abbreviation: ND, no resistance variants were detected.

*Resistance testing was performed at baseline and during the vaniprevir dosing period (28 days) in patients with predefined treatment failure and HCV RNA ≥1,000 U/mL.

†Range ±2 weeks.

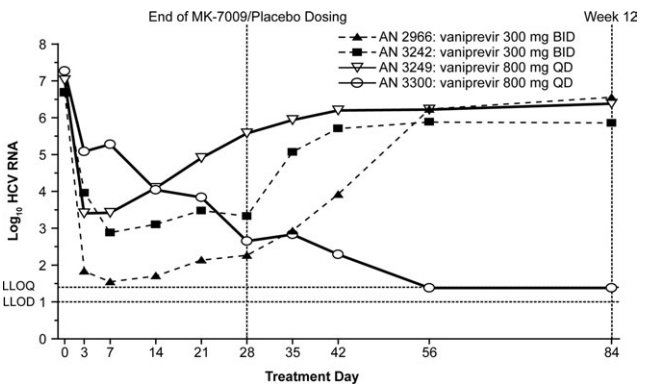

Fig. 3. HCV RNA levels in selected patients who received vaniprevir with resistance variants detected. Vaniprevir was dosed for 28 days in combination with Peg-IFN-α-2a and RBV, which were continued for an additional 44 weeks. All doses were given in combination with Peg-IFN-α-2a and RBV. AN, allocation number; LLOQ, lower limit of quantification (25 copies/mL); LLOD, lower limit of detection (10 copies/mL).

Table 5. Most-Common Adverse Events With Onset During Vaniprevir Treatment and 14-Day Follow-up (Incidence >20% in One or More Treatment Groups)

	Placebo + Peg-IFN-α-2a + RBV (n = 19)	Vaniprevir 300 mg BID + Peg-IFN-α-2a + RBV (n = 18)	Vaniprevir 600 mg BID + Peg-IFN-α-2a + RBV (n = 20)	Vaniprevir 600 mg QD + Peg-IFN-α-2a + RBV (n = 18)	Vaniprevir 800 mg QD + Peg-IFN-α-2a + RBV (n = 19)
Patients with ≥1 AE	18 (94.7)	15 (83.3)	18 (90.0)	16 (88.9)	18 (94.7)
Drug-related* AE	15 (78.9)	15 (83.3)	18 (90.0)	15 (83.3)	17 (89.5)
AEs					
Abdominal pain (upper)	3 (15.8)	1 (5.6)	2 (10.0)	4 (22.2)	2 (10.5)
Diarrhea	4 (21.1)	1 (5.6)	6 (30.0)	2 (11.1)	4 (21.1)
Dyspepsia	4 (21.1)	4 (22.2)	0 (0.0)	2 (11.1)	4 (21.1)
Nausea	5 (26.3)	5 (27.8)	8 (40.0)	7 (38.9)	6 (31.6)
Vomiting	0 (0.0)	0 (0.0)	8 (40.0)	3 (16.7)	3 (15.8)
Fatigue	7 (36.8)	3 (16.7)	7 (35.0)	4 (22.2)	2 (10.5)
Influenza-like illness	4 (21.1)	4 (22.2)	4 (20.0)	4 (22.2)	5 (26.3)
Pyrexia	2 (10.5)	0 (0.0)	1 (5.0)	1 (5.6)	4 (21.1)
Decreased appetite	2 (10.5)	4 (22.2)	5 (25.0)	2 (11.1)	1 (5.3)
Headache	7 (36.8)	4 (22.2)	9 (45.0)	8 (44.4)	4 (21.1)
Insomnia	2 (10.5)	4 (22.2)	1 (5.0)	3 (16.7)	2 (10.5)
Rash	4 (21.1)	2 (11.1)	2 (10.0)	3 (16.7)	2 (10.5)

Every patient was counted a single time for each specific AE.

*Drug related indicates that the investigator believed the AE was related to vaniprevir/placebo, Peg-IFN, and/or RBV.

vaniprevir reported an AE of vomiting (mild, n = 12; moderate, n = 2). The time to onset ranged between days 1 and 27, with no clear relationship between dose and onset of vomiting.

There were no serious AEs or treatment discontinuations resulting from an AE during the vaniprevir dosing period, and there were no deaths. Ten serious AEs were reported in 9 patients; however, all became apparent after completion of the vaniprevir dose period and 14-day safety follow-up period. None of these serious AEs was considered by the investigator to be related to vaniprevir or placebo. There were also no clinically meaningful differences in vital signs or in ECG parameters between treatment groups during the vaniprevir treatment and 14-day safety follow-up period. Changes in laboratory values were generally comparable between vaniprevir and placebo (Supporting Table 2).

Discussion

The first HCV protease inhibitors approved recently (boceprevir and telaprevir) have strong antiviral potency, but have to be given every 8 hours with fatty meals and add to the side-effect profile of Peg-IFN-α plus RBV. Anemia, dysgeusia, and skin rashes have been variously associated with boceprevir and/or telaprevir.[4,6] Vaniprevir 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.[17,18]

In the present phase II study, patients receiving vaniprevir achieved significantly higher rates of RVR, compared to placebo, regardless of dose or administration frequency. The highest rates of RVR were reported in patients receiving the higher doses of vaniprevir of 600 mg BID or 800 mg QD (79% and 83%, respectively), compared to 5.6% in the placebo control arm. Patients in all four vaniprevir treatment arms also achieved numerically higher EVR and SVR results, compared to the control arm; however, these differences were not statistically significant because of the low number of enrolled patients and the high rates of SVR observed for the placebo control arm. In addition, the study was not powered to assess differences in rates of SVR between treatment arms. Regardless, these data suggest that the addition of vaniprevir to a Peg-IFN-α plus RBV backbone for 4 weeks, followed by 44 weeks of Peg-IFN-α plus RBV, results in improved rates of SVR, compared with Peg-IFN-α plus RBV alone, although the optimum duration of HCV protease inhibitor therapy is almost certainly longer than 4 weeks, and extending vaniprevir treatment duration may result in further improvements in SVR rates.[9] Alternatively, achieving SVR rates >70% with a relatively short 28-day treatment duration of vaniprevir may be considered advantageous and of particular benefit in patients who do not tolerate direct-acting antiviral agents. With a greater than $5\log_{10}$ reduction in HCV RNA levels from baseline after 4 weeks of therapy, vaniprevir also appears to be as potent as other first- or second-wave HCV protease inhibitors, such as boceprevir,[4] telaprevir,[6] BI 201335,[13] TMC 435,[14,15] and ITMN 191.[16]

An SVR rate of 63% among control patients receiving Peg-IFN-α-2a plus RBV alone in the present study

is consistent with similarly high rates of SVR reported with standard-of-care regimens in several other recently presented studies of new anti-HCV drugs. Other examples include the PILLAR phase 2 study with TMC 435[20] and alisporivir, a cyclophilin A inhibitor.[21] Studies of this type are often performed in recognized tertiary referral centers that have extensive experience in the management of side effects associated with Peg-IFN-α plus RBV therapy, permitting optimal RBV dosing that, in turn, contributes to better treatment outcomes. The exclusion of patients with cirrhosis from this study, as well as the small sample size, could also have contributed to a higher SVR rate in the control group. In addition, although *IL28B* genotype did not correlate with treatment outcome for the control or experimental groups in this study, the lack of statistically significant association was not unexpected, given the small sample size.

Although the duration of drug administration was limited to 28 days in the present study, the safety profile of vaniprevir was encouraging. The observation period for safety analysis consisted of 28 days of vaniprevir exposure plus 14 days of follow-up. During this period, there were no serious AEs leading to discontinuation of therapy, and the frequency of AEs was comparable between vaniprevir and control arms. Vomiting was reported more frequently in the vaniprevir 600-mg BID group than in the placebo group, but there was no clear relationship between dosing and onset of vomiting, which was mild in all but 2 cases. AEs frequently reported with other members of first- and second-wave HCV protease inhibitors, including anemia, rash, dysgeusia, and elevated bilirubin levels, did not differ significantly between vaniprevir and placebo groups.

Resistance is an important consideration when using HCV protease inhibitors.[22] RAVs that cause a decreased sensitivity to several first-generation protease inhibitors have been identified in patients preceding treatment with HCV protease inhibitors. This study employed population sequencing, which can detect minor species that exist at frequencies of >25% in the circulating population. The D168E variant was observed in viruses isolated from 1 patient at baseline who exhibited a slow decline in HCV RNA levels during the vaniprevir/Peg-IFN-α-2a/RBV dosing period. This variant has been shown to have a 10-fold lower sensitivity to vaniprevir *in vitro* and hence could explain the slower decrease in HCV RNA observed in this patient.[17] No other vaniprevir RAVs were identified in baseline samples by population sequencing.

In the present study, RAVs were identified at NS3 positions R155 and D168 during the vaniprevir dosing period in 3 patients who met the protocol-defined failure criteria. Variants at positions R155 and D168 are known to cause decreased sensitivity to vaniprevir *in vitro*[17] and have also been reported on previously in studies of other HCV protease inhibitors.[23-26] The R155K variants were not observed in patients with genotype 1b infection who exhibited virologic failure in this study or in previous clinical studies.[27] This can be partly explained by the fact that the codon-encoding lysine at position 155 in the genotype 1b virus requires two base-pair (bp) changes from the baseline arginine codon, but only a single bp change in genotype 1a viruses.

In conclusion, vaniprevir is a highly potent second-wave HCV protease inhibitor with a predictable resistance and a favorable safety profile that is suitable for QD or BID administration. The rates of RVR described in this study are among the highest reported for HCV protease inhibitor-based triple therapies, and although patients with cirrhosis were excluded from this study and the duration of vaniprevir exposure was limited to 28 days, the observed safety profile was reassuring. Furthermore, there were only a limited number of treatment failures associated with the appearance of previously described HCV NS3/4A RAVs. However, the number of patients enrolled in this phase II study was limited, and therefore vaniprevir dosing will be extended in future studies to further define treatment regimens that yield optimized antiviral effects. These future studies will consider whether vaniprevir-based regimens are comparable or superior to other HCV protease inhibitor-based triple therapies with regard to efficacy, safety, tolerability, or treatment duration. Based on the results of this study, vaniprevir should be further developed for HCV protease inhibitor-based triple therapies. Vaniprevir is also a promising candidate for inclusion within future all-oral anti-HCV strategies.

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