Virologic Resistance Analysis From a Phase 2 Study of MK-5172 Combined With Pegylated Interferon/Ribavirin in Treatment-Naive Patients With Hepatitis C Virus Genotype 1 Infection

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(See the Major Article by Svarovskaia et al on pages 1666–74, and the Editorial Commentary by Tong and Kwong on pages 1675–7.)

Background. Virologic failure following treatment of hepatitis C virus (HCV) genotype 1 with direct-acting antiviral agents is often accompanied by the emergence of resistant variants. MK-5172 is an investigational once-daily protease inhibitor. We analyzed variants in treatment-naive noncirrhotic patients with virologic failure on MK-5172 (100–800 mg/day) plus pegylated interferon alfa/ribavirin (peg-IFN/RBV) during a phase 2 trial.

Methods. Population and selective clonal sequencing were performed at baseline and at virologic failure in the 4 MK-5172 dosing arms. MK-5172 activity was determined using a mutant replicon assay.

Results. Six of 266 (2.3%) MK-5172 recipients satisfied prespecified criteria for virologic failure, all with genotype 1a infection. Five patients with virologic failure were in the MK-5172 100-mg arm, including 4 patients with low plasma MK-5172 levels documented during triple therapy. Variants associated with >4-fold loss of potency were detected in 3 of the 4 patients with genotype 1a breakthrough while on MK-5172. The fifth patient had undetectable HCV-RNA levels at the end of triple therapy but subsequently broke through during the peg-IFN/RBV tail 16 weeks after completion of MK-5172. Three patients had D168 variants at virologic failure, including 2 with the D168A variant associated with a 95-fold loss of potency. The sole apparent relapse was actually a genotype 3a reinfection in the MK-5172 200-mg group.

Conclusions. Virologic failure occurred uncommonly (6/266 [2.3%]) in MK-5172/peg-IFN-RBV recipients. The most prevalent treatment-emergent variants were detected at the D168 locus. D168A variants conferring approximately 2-log reduction in MK-5172 susceptibility emerged in 2 of the 4 evaluable patients with genotype 1a breakthrough. Clinical Trials Registration. NCT01353911.

Keywords. MK-5172; hepatitis C genotype 1; treatment-naive; resistance-associated variants.

Virologic resistance in hepatitis C virus (HCV)-infected patients treated with direct-acting antiviral agents is often accompanied by the emergence of resistance-associated variants (RAVs) [1–8]. Rapid viral turnover coupled with an error-prone RNA-dependent RNA-polymerase generates quasi-species of genetically related viruses harboring minor genomic differences. Prior to treatment with direct-acting antiviral agents, polymorphic variants associated with decreased susceptibility to some drugs are likely present at low levels even when undetectable by standard population sequencing. RAVs can emerge under selective drug pressure when viral replication is incompletely suppressed [9–13]. Emergent variants have generally lower replication capacity than the predominant wild-type viruses and typically become undetectable over time once therapy is stopped [14].
MK-5172 is an investigational macrocyclic NS3/4A protease inhibitor active against multiple HCV genotypes [15]. In a recent dose-ranging trial of response-guided therapy, MK-5172 for 12 weeks combined with either 24 or 48 weeks of pegylated interferon alfa plus ribavirin (peg-IFN/RBV) significantly improved sustained virologic response (SVR) rates in treatment-naive noncirrhotic patients with HCV genotype 1 infection compared with similar patients given boceprevir plus peg-IFN/RBV [16]. The SVR rate at follow-up week 24 for the 266 patients comprising the 4 combined MK-5172 groups ranged from 86% to 93% across dosing arms, compared with 61% for the 66 control patients in the boceprevir arm. We describe the baseline and emergent variants detected in the 6 (2.3%) MK-5172 recipients with virologic failure.

METHODS

Study Design
MK-5172 Protocol-003 was a randomized, active-control, double-blind, multicenter study to estimate the efficacy of 4 response-guided dosing regimens of MK-5172 combined with peg-IFN/RBV relative to boceprevir plus peg-IFN/RBV in treatment-naive noncirrhotic patients with chronic HCV genotype 1 infection [16]. Previously untreated adult patients with chronic HCV genotype 1 infection were eligible if their screening HCV RNA level was $\geq 10^4$ IU/mL. Participants received MK-5172 once daily at doses of 100 mg, 200 mg, 400 mg, or 800 mg for 12 weeks along with peg-IFN/RBV. Peg-IFN/RBV alone was then continued for 12 or 36 additional weeks depending on whether HCV RNA was undetectable at week 4. Patients treated with $\geq 1$ dose of any study medication served as the primary population for the analyses. Plasma levels of MK-5172 and ribavirin were measured in participants providing consent for the optional nested pharmacokinetic substudy.

After treatment week 4, a patient’s response was considered a virologic failure if the patient satisfied the stopping rules (“futility”), had $1\log_{10}$ increase in HCV RNA level from their nadir while on treatment (“rebound”), had quantifiable HCV RNA after becoming undetectable while on treatment (“breakthrough”), or had detectable HCV RNA after having undetectable HCV RNA at the end of therapy (“relapse”). Early stopping rules for futility were prespecified as a HCV RNA level $\geq 100$ IU/mL at week 12 or quantifiable HCV RNA at week 24. Patients discontinued from study therapy for nonvirologic reasons, such as adverse events, withdrawal of consent, and loss to follow-up, were counted among all-cause failures in computing SVR rates in the primary modified intent-to-treat analysis.

Viral and Resistance Assays
Plasma HCV RNA levels were quantified by the COBAS TaqMan HCV Test, version 2.0 with the High-Pure System (Roche Diagnostics, Branchburg, New Jersey), with respective lower limits of detection and quantification of 15.1 and 25 IU/mL. HCV RNA was isolated at baseline and near the time of virologic failure. Genotyping was conducted using Versant HCV genotyping (LiPA) 2.0 (Innogenetics). Ambiguous genotypes were further confirmed by amplification of a conserved NS5B region containing 392 base pairs [17].

To assess genotypic variation at baseline or at the time of virologic failure, the NS3/4A gene was amplified from samples with RNA levels $\geq 1000$ IU/mL using reverse transcription polymerase chain reaction (PCR) followed by population and selective clonal sequencing. For clonal sequencing, PCR amplification was only performed on the NS3 protease region (amino acids 1–181), and the resultant amplicons were cloned into a TOPO TA vector (Invitrogen). At least 33 clones (typically $\geq 40$ clones) were sequenced at each time point. Resultant amino acid sequences were compared to wild-type HCV genotype 1a (H77) or 1b (Con1) reference sequences. Single N3A-protease amino acid substitutions including V36M, T54S, Q80K, S122R, R155K, D168A/E/T/V/Y, or I170T in genotype 1a and V36A, T54A/S, V55A, Q80R, R155K/Q, A156G/S, D168A/E/H/T/V, or V170A in genotype 1b were considered clinically relevant because these mutations had been commonly identified after treatment failures with protease inhibitor regimens [18–26]. The unexpected discovery of genotype 3a in one patient posttherapy infected at entry with genotype 1a was interrogated by deep sequencing with primers to highly conserved regions of NS5B using Nextera XT-Illumina technology. The reference sequence for identification of genotype 3a was S52.

For phenotypic analyses, MK-5172 antiviral potency was measured in stable Huh-7 cell lines harboring subgenomic replicons encoding NS3 mutations engineered through site-directed mutagenesis [15]. Fold-shift for each variant was measured relative to the effective concentration to inhibit growth by 50% (EC$_{50}$) against the wild-type replicon. In vitro fitness for RAVs was determined by the number of colonies that survived transfection and antibiotic selection (Geneticin, G418) relative to the wild-type replicon [27].

RESULTS

Subject Characteristics
Among 264 MK-5172 recipients with genotype 1a or 1b infection, SVR$_{24}$ rates were 134 of 158 (84.8%) for infections with subtype 1a and 103 of 106 (97.2%) for infections with subtype 1b; 2 additional patients were infected with subtype 1d or 1h. Of the 66 patients treated with 100 mg/day of MK-5172, 59 (89%) achieved SVR$_{24}$. A total of 6 (2.3%) patients from the composite MK-5172 groups did not achieve SVR$_{24}$ and satisfied predetermined criteria for virologic failure (Table 1). Five of the 6 virologic failures in the study were in 100-mg dosing arm, while the
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Abbreviations: HCV, hepatitis C virus; peg-IFN/RBV, pegylated interferon/ribavirin; SVR24, sustained virologic response 24 weeks after discontinuation of therapy; WT, wild type.

* Treatment consisted of triple therapy with peg-IFN/RBV using a response-guided schedule. Five of the 6 virologic failures in the study were in arm 1 (100-mg dose), while the other virologic failure occurred in arm 2 (200-mg dose).

b All polymorphisms detected at amino acid positions 36, 80, 122, 155, 156, and 168 of the NS3 protease are tabulated here. Full clonal sequences are given in Supplementary Table 1.

c Four (A–D) of these 5 patients had low or undetectable plasma MK-5172 levels prior to viral breakthrough; the other patient (E) had completed the prescribed course of MK-5172 before breakthrough viremia.

d Patient D was lost to follow-up subsequent to virologic failure.

e Patient E achieved undetectable HCV RNA levels while on 100 mg of MK-5172 but experienced viral breakthrough 16 weeks after MK-5172 was discontinued on day 204 of peg-IFN/RBV treatment.

f Patient F was apparently reinfected or superinfected with HCV subtype 3a, which could not be detected at baseline by several methods.

g HCV subtype 1a RNA could not be identified at follow-up by deep sequencing.
other virologic failure occurred in the 200-mg dosing arm. All virologic failures occurred in patients infected with HCV genotype 1a whose IL28B genotype was CT.

**Pretreatment Variants**

Population NS3-sequence data were obtained at baseline or screening from 261 (98.9%) of the 264 patients infected with genotype 1a or 1b randomized to the 4 MK-5172 arms. Although treatment-naïve, a total of 73 of the 261 evaluable MK-5172 recipients (28.0%) harbored variants at entry associated with clinical resistance to at least 1 other protease inhibitor (Supplementary Table 1). Nonetheless, 70 (95.9%) achieved SVR24 (n = 67) or target not detected at their last visit (n = 3).

Baseline virus from 64 of the 155 (41.3%) evaluable MK-5172 recipients with genotype 1a infections contained the Q80K polymorphism (which has been associated with failure in genotype 1a infections treated with recently licensed simeprevir-based combination regimens [21]). Treatment with MK-5172 plus peg-IFN/RBV resulted in SVR24 in 58 of the 64 patients (90.6%) infected with the Q80K genotype 1a variant at baseline. Only 1 patient harboring Q80K at baseline (patient B with 100% of the double mutant V36L_Q80K) had protocol-defined virologic failure.

**Pretreatment Variants and Subsequent Virologic Failure**

None of the 6 MK-5172 recipients who developed protocol-defined virologic failure harbored pretreatment variants detected by population sequencing with ≥4-fold decreased potency to MK-5172 compared to wild-type virus in the replicon assay. V36L (which as a single substitution conferred approximately 2-fold decreased potency) and I170V polymorphisms were identified at baseline by population sequencing in 1 patient each with later virologic failure (patients B and F, respectively).

Complete clonal sequences of the genotype-1a quasi-species present on entry in the 6 MK-5172 recipients with protocol-defined virologic failure are given in Supplementary Table 2. Low levels of R155K (5%) and S122G (6%) were detected at baseline in patients A and D, respectively. In addition, 2 other patients (B and C) had high levels of baseline polymorphisms at positions 36 and 122: patient B had 100% V36L_Q80K with 2% S122C and 2% D168G, and patient C had 100% S122N with 2% R155G and 2% D166G. Substitutions of V36L_Q80K or R155K caused approximately 2-fold and approximately 4-fold increases in the EC₅₀ of MK-5172, respectively, whereas D168G as a single mutant conferred 11-fold increased EC₅₀. The activity of MK-5172 against S122 variants remains to be determined (Table 2).

**Virologic Failure, Plasma MK-5172 Levels, and Emergent Variants**

Five of the 6 protocol-defined virologic failures were in the MK-5172 100-mg dosing arm (Figure 1). Compared with the median trough plasma levels measured in the pharmacokinetic substudy as well as relative to drug levels early in their treatment courses, 4 of these 5 patients had documented low or undetectable plasma MK-5172 concentrations while still receiving triple therapy during the initial 12 weeks of the study prior to viral breakthrough (Supplementary Table 3).

Genotype 1a variants with reduced susceptibility to MK-5172 were detected in 3 of 4 evaluable patients (A, C, and E, but not B) by clonal sequencing after virologic failure in the MK-5172 100-mg group. Viruses from patients A and B were largely wild-type at the time of failure, although clonal sequencing in patient A transiently demonstrated <5% of the V36A/M, R155K, and D168G variants. Patient C had viral mixtures of 11% R155K/S and 7% D168A/E/K at failure, but only 2% R155K and 2% D166G were identified at these loci 20 days after treatment discontinuation. Virus from patient D could not be evaluated because the HCV RNA level was <1000 copies/mL at the time of

![Table 2. In Vitro Activity of MK-5172 Against Replicon Variants With Common Resistance-Associated Mutations Selected by Protease Inhibitors](https://academic.oup.com/cid/article-abstract/59/12/1657/2895498/Downloaded_from_Https://academic.oup.com/cid/article-abstract/59/12/1657/2895498)
Figure 1. Time course of emerging variants in the 6 MK-5172 recipients with protocol-defined virologic failure. Interpolated red circles indicate the measured hepatitis C virus RNA levels over time from baseline through follow-up. Plasma MK-5172 levels (blue squares) were assayed in 5 patients (A–D, F) at various time points, and were undetectable on at least 1 measurement in 3 of these patients. For reference, the steady-state geometric mean trough concentration for 35 patients from the MK-100 mg arm enrolled in the nested pharmacokinetic study was 26 nM (90% confidence interval, 22–31 nM). The limit of quantification for the assay was <5 nM MK-5172. The axes in the panels are drawn to different scales. The 3 patients with virologic failure who had achieved rapid virologic response are so labeled. Treatment-emergent variants are shown in the pie charts if the mutations were detected in
failure and the patient was then lost to follow-up. Patient E had achieved undetectable HCV RNA levels when receiving 100 mg of MK-5172 with peg-IFN/RBV but subsequently experienced viral breakthrough on day 204 of peg-IFN/RBV treatment 16 weeks after MK-5172 dosing was completed. Virus recovered at virologic failure in this patient was highly enriched for the D168A substitution (98%), which conferred a 95-fold potency loss to MK-5172 in vitro. Wild-type virus largely replaced the mutant virus over time off therapy, and within 5 months the D168A mutant was only found in 1 of the 40 tested clones.

The single patient (F) with protocol-specific virologic "relapse" in the 200-mg MK-5172 group was originally infected with genotype 1a but actually had a reinfection with genotype 3a shortly after all therapy was completed. Genotype 1a could not be demonstrated at the time of virologic failure. Instead, a gene fragment could be amplified from a set of genotype 3a–specific primers (Table 3). Taking advantage of a conserved region within the NS5B gene that allows amplification of all HCV genotypes, a mini-amplicon containing 392 base pairs indicated that the fragment derived from genotype 3a. To explore whether a low level of genotype 1a virus was being masked by a high level of genotype 3a virus, deep NS3/4A sequencing was conducted on samples obtained at virologic failure. Genotype 1a could not be detected by deep sequencing with genotype 1a primers. Phylogenetic analysis confirmed the unique sequence belonged to genotype 3a.

Variants in Discontinued Patients Without Virologic Failure

Five additional patients treated with MK-5172 prematurely discontinued therapy for nonvirologic reasons. Sequencing data were obtained at later time points from 3 of these patients with genotype 1a infections. In 2 cases with undetectable HCV-RNA at the time of discontinuation, no MK-5172 RAVs were found when the viral load eventually rebounded off-treatment. The third subject discontinued after 3 days of therapy, but later returned for follow-up. Baseline sequencing of 40 clones had revealed a V29A_T40A_Q80K_S91T_V151A_L153I variant in 39 clones along with 1 clone harboring D168G. At the first follow-up visit on study day 36, circulating virus was comprised of 77% D168E and 12% R155K variants, which disappeared rapidly over time. By day 92 (58 days later), the percentage of D168E variants had fallen to 23% and R155K was no longer identified. By day 411, the viral population had completely reverted to wild type (Figure 2).

Phenotypic Susceptibility

Wild-type and variant susceptibilities to MK-5172 in the replicon assay varied by genotype (Table 2). For example, the potency loss conferred by the D168A mutation was 95-fold for genotype 1a vs approximately 14-fold for genotype 1b. Of the tested genotype 1a replicons with single amino acid substitutions, only the D168A, D168E, D168G, and R155K replicons exhibited >4-fold decreased MK-5172 susceptibility compared to wild type. Although the double mutant V36L_Q80K exhibited a 2.5-fold increase in EC50, the triple mutant V36L_Q80K_R155S raised the EC50 71-fold over the wild-type genotype 1a replicon. Single substitutions at the D168 locus in genotype 1b replicons to A, G, or K (but not to E) conferred >4-fold decreased MK-5172 susceptibility. MK-5172 retained appreciable in vitro
activity (<4-fold increase in EC_{50}) against many common variants selected at virologic failure by other protease inhibitors. Other than the D168E genotype 1a replicon, tested variants were less fit than wild-type virus in our assay system.

**DISCUSSION**

The parent phase 2 study evaluated 4 response-guided treatment regimens combining MK-5172 with peg-IFN/RBV relative to response-guided therapy with boceprevir and peg-IFN/RBV in treatment-naive noncirrhotic patients infected with HCV genotype 1 [16]. Patients treated with MK-5172 at all doses achieved significantly higher SVR rates than boceprevir recipients. Even though 28% of MK-5172 recipients harbored pretreatment variants selected by other protease inhibitors, there was a low rate of virologic failure among patients treated with MK-5172 and peg-IFN/RBV. Only 6 of 266 (2.3%) MK-5172 recipients developed protocol-defined virologic failure, all of whom were infected with genotype 1a. Variants with >2-fold increased EC_{50} to MK-5172 in a replicon assay were detected in all 4 patients with post-failure genotype 1a sequencing data, including substitutions at D168 conferring high-level MK-5172 resistance in vitro. Relative to wild type, replicons expressing these mutations were unfit. The low MK-5172 concentrations in 4 patients who subsequently developed breakthrough viremia suggest that virologic failure resulted in large part from medication nonadherence, but other possibilities (such as malabsorption and/or induced metabolism of MK-5172) cannot be totally excluded as contributing factors. The 100-mg dose may be less forgiving of poor compliance than higher doses of MK-5172, especially when adherence to peg-IFN/RBV is also erratic. Functional monotherapy with MK-5172 at suboptimal plasma concentrations could have facilitated the emergence of RAVs.

Consistent with the clinical observations, MK-5172 retained significant in vitro activity against many common genotype 1 RAVs selected by other protease inhibitors, including boceprevir, telaprevir, vaniprevir, and simeprevir [15, 18–25]. For the most part, replicons with single amino acid substitutions were tested in our assay and the phenotypic impact of multiple mutations in the same virus was only selectively tested. MK-5172 inhibits the NS3/4A protease of multiple HCV genotypes in vitro, including genotypes 1a/b, 4a, 6a, 5a, 2a/b, and 3a (in decreasing order of potency) [15]. Nonetheless, trough plasma levels of MK-5172 in compliant patients dosed at 100 mg once daily would be expected to exceed the EC_{50} for genotype 3a. Curiously, in patient F cured of the initial genotype 1a infection despite suboptimal adherence to study medication, an apparent reinfection with genotype 3a became manifest 4 weeks after the peg-IFN/RBV tail of a MK-5172 regimen was completed (16 weeks following discontinuation of MK-5172) [28].

Not all baseline and emergent viral variants will actually confer drug or class resistance, but sufficient clinical correlation and phenotypic data must accumulate before interpretive guidelines for genotypic resistance testing can be established. RAVs need to be distinguished from therapeutically insignificant polymorphisms, but how best to make this distinction is not straightforward without extensive clinical experience. Historically, any mutation emerging under selective drug pressure was generally assumed to confer some degree of resistance. Inhibitory drug concentrations for emergent variants can be assessed in vitro relative to values for wild type, but what constitutes a therapeutically meaningful fold change in EC_{50} or EC_{90} is not self-evident. Absolute inhibitory drug concentrations can be compared to achievable drug levels, although plasma pharmacokinetic parameters may not be as relevant as the concentrations achieved intracellularly. Meaningful clinical cutoffs for phenotypic resistance

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**Figure 2.** Evolution of genotype 1a variants in a MK-5172 recipient who discontinued study therapy after 3 days. Clonal sequencing in this patient at baseline had disclosed 1 clone harboring D168G. The patient discontinued the MK-5172 regimen after 3 days but later returned for follow-up. At the first follow-up visit on study day 36, circulating virus was comprised of the 77% D168E and 12% R155K, both of which disappeared rapidly over time. By day 92 (58 days later), the percentage of D168E variants was reduced to 23% and R155K was not identified. By day 411, no D168 variants were detected. Extrapolating from the replicon data, the transient posttherapy D168E variant was both more susceptible to MK-5172 and fit than the pretreatment D168G variant. Abbreviation: WT, wild type.
The recent Food and Drug Administration approval of simeprevir in the United States was largely based on the results of 2 phase 2B studies (PILLAR and ASPIRE) and 3 phase 3 trials (QUEST 1, QUEST 2, and PROMISE) conducted in treatment-naive and treatment-experienced patients with chronic HCV genotype 1 infection [21–25]. The efficacy of simeprevir in patients with the common Q80K substitution at baseline was lower than in patients without this polymorphism. In our study, 58 (91%) of the 64 MK-5172 recipients infected with genotype 1a harboring the Q80K variant at baseline achieved SVR24. Structural modeling of the NS3 protease-bound MK-5172 suggests that the flexible P2-substituent of MK-5172 is distal to Q80 and therefore unlikely to be affected by the polymorphism at this position [29,30]. In contrast, simeprevir has an extended P2-substituent such that substitution of Q80K might alter the molecular confirmation and consequently affect binding affinity [29,30]. The presence of a Q80 polymorphism did not appear to impact treatment outcomes with MK-5172.

The role of resistance testing requires further study as the use of direct-acting antiviral agents for chronic HCV infection becomes widespread [12,31]. RAVs could become increasingly relevant as interferon-sparing drug combinations replace interferon-based regimens [32]. The lower resistance barrier for protease inhibitors in subtype 1a than 1b may make sequencing particularly informative in subtype 1a infections [13,18]. As with human immunodeficiency virus (HIV), resistance may develop to some but not all drugs within a class [15]. Unlike HIV infection where resistant virus is archived indefinitely, the long-term implications of transient RAVs after failed treatment for HCV remain uncertain [14,31]. Timing of retreatment may be a critical factor in determining whether emergent RAVs will adversely affect the next regimen. Because combination therapy is always recommended, low baseline levels of protease inhibitor RAVs might impact outcome only when poor interferon responsiveness, decreased susceptibility to other coadministered antiviral agents, or erratic compliance with an unforgiving regimen is concurrently present.

Early treatment discontinuation in patients unlikely to achieve SVR could decrease the frequency and complexity of RAVs selected by a failing regimen [18]. To preempt selection of RAVs as well as minimize unnecessary cost and toxicity, direct-acting antiviral-based regimens should be discontinued promptly any time virologic failure becomes evident through periodic monitoring of HCV RNA levels during treatment. Nonetheless, a transient MK-5172 RAV emerged subsequent to only 3 days of treatment in a noncompliant patient from our study.

Virologic failure was encountered infrequently in MK-5172 recipients in our dose-ranging study and occurred exclusively in genotype 1a infections. All 4 patients with viral breakthrough during the MK-5172 dosing period had low or undetectable MK-5172 levels at times. The most prevalent treatment-emergent RAVs were D168X, including the D168A substitution associated with 2-log decrease in MK-5172 activity in vitro. These variants became less prevalent over time after selective drug pressure was removed, suggesting that D168 variants were less competitively fit than wild-type virus. Many RAVs selected by other protease inhibitors do not appear to be cross-resistant to MK-5172. Ongoing studies will define the efficacy of MK-5172-based regimens in a broad population of HCV-infected patients.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We are indebted to all the patients, healthcare providers, and investigators involved with the parent study. The contributions of Daria Hazuda, Donald Graham, Frank Dutko, Victoria Ennewadu, and Irene Pak of Merck are much appreciated. We are likewise grateful to Karyn Davis from Merck for technical assistance in the preparation of this manuscript.

Disclaimer. A penultimate version of the manuscript was reviewed by the sponsor. Authors had full access to all pertinent data upon request. Each author approved an essentially final version of the manuscript. The opinions expressed in this report represent the consensus of the authors and do not necessarily reflect the formal position of Merck.

Financial support. This work was supported by Merck.

Potential conflicts of interest. Merck is developing MK-5172 for therapeutic use in patients with HCV infection. The company sponsored and funded P003 and the associated analyses. As employees of Merck, all authors own stock and/or stock options in the company.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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