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Efficacy and Safety of a Two-Drug Direct-Acting Antiviral Agent Regimen Ruzasvir 180 mg and Uprifosbuvir 450 mg for 12 Weeks in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 3, 4, 5, or 6

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Abbreviation List:

AEs - adverse events
ALT - alanine aminotransferase
APRI - aspartate aminotransferase to platelet ratio index
AST - aspartate aminotransferase
CI - confidence interval
DAAs - direct-acting antiviral agents
FAS - full analysis set

29 FW - follow-up week
30 GT - genotype
31 HCV - hepatitis C virus
32 HIV - human immunodeficiency virus
33 LLoQ - lower limit of quantitation
34 NS3/4A - nonstructural protein 3/4A
35 NS5A - nonstructural protein 5A
36 NS5B - nonstructural protein 5B
37 PP - per-protocol
38 RAP - resistance analysis population
39 RAS - resistance-associated substitution
40 SVR – sustained virologic response
41 SVR12 - sustained virologic response at 12 weeks after the completion of study therapy
42 TW - treatment week
43
44

Abstract

Ruzasvir (MK-8408, an NS5A inhibitor) and uprifosbuvir (MK-3682, a nonstructural protein 5B nucleotide inhibitor) are highly potent direct-acting antiviral agents for the treatment of hepatitis C virus (HCV) infection. A phase III clinical trial evaluating the two-drug combination of ruzasvir 60 mg plus uprifosbuvir 450 mg suggested suboptimal efficacy in certain HCV genotypes (C-BREEZE 1; NCT02759315). The aim of the present study was to evaluate the efficacy and safety of ruzasvir in combination with uprifosbuvir administered at a higher dose than that assessed in the earlier study (C-BREEZE 2: NCT02956629 /Merck protocol PN041). Treatment-naïve or interferon (with or without ribavirin)–experienced participants with or without compensated cirrhosis were enrolled. All participants received ruzasvir

180 mg plus uprifosbuvir 450 mg once daily for 12 weeks. The primary objectives were the proportion of participants with HCV RNA <15 IU/mL at 12 weeks after the end of study therapy (SVR12), and safety and tolerability of the study drug. Overall, 282 participants were enrolled. SVR12 (n/N) was 91.3% (42/46) in participants infected with HCV genotype (GT) 1a; GT1b, 96.7% (29/30); GT2, 91.5% (43/47); GT3, 73.8% (45/61); GT4, 98.2% (55/56); GT5, 100.0% (18/18); GT6, 90.9% (20/22). Adverse events (AEs) were reported by 61.3% of participants; drug-related AEs were reported by 33.3%. The most frequent ($\geq 5\%$ of participants) drug-related AEs in all participants were fatigue (7.8%) and headache (7.4%). In conclusion, the two-drug combination of ruzasvir 180 mg plus uprifosbuvir 450 mg for 12 weeks was highly effective and well-tolerated in participants infected with HCV GT1, GT2, GT4, GT5, and GT6, with a lower efficacy in GT3-infected persons.

Keywords: hepatitis C virus; clinical trial; genotype; safety; efficacy

The development of direct-acting antiviral agents (DAAs) has transformed the treatment of hepatitis C virus (HCV) infection,¹ and pangenotypic regimens are now available that result in high rates of sustained virologic response (SVR) across all HCV genotypes (GT).² Treatment options have transitioned from genotype-specific regimens such as sofosbuvir/ledipasvir,³ elbasvir/grazoprevir,⁴ and paritaprevir/ombitasvir/ritonavir/dasabuvir⁵ to pangenotypic regimens such as glecaprevir/pibrentasvir⁶ and sofosbuvir/velpatasvir.⁷ An additional regimen under investigation for pangenotypic activity is the combination of ruzasvir/uprifosbuvir.

Ruzasvir (MK-8408) is a potent HCV nonstructural protein 5A (NS5A) complex inhibitor.⁸ In vitro, it retains activity against RASs selected by first-generation NS5A inhibitors in individuals infected with HCV GT1a.⁸ Uprifosbuvir (MK-3682) is a potent HCV NS5B polymerase nucleotide inhibitor with pangenotypic activity in vitro and a high barrier to resistance. The safety and efficacy of ruzasvir, uprifosbuvir, and the nonstructural protein 3/4A protease inhibitor grazoprevir was explored in the phase 2 C-CREST studies (ClinicalTrials.gov numbers NCT02332707 and NCT02332720).⁹⁻¹¹ In these studies, the three-drug regimen of ruzasvir 60 mg and uprifosbuvir 450 mg in combination with grazoprevir 100 mg, with or without ribavirin, demonstrated high efficacy and excellent tolerability in a broad population that included treatment-naïve and prior interferon-experienced, cirrhotic and noncirrhotic

participants with HCV GT1-6 infection, and also participants who had experienced virologic relapse after treatment with all-oral DAA regimens.⁹⁻¹¹ Given the high efficacy of ruzasvir/uprifosbuvir/grazoprevir, the relative contribution of grazoprevir was evaluated in a phase II nonrandomized study by evaluating the two-drug regimen of ruzasvir 60 mg and uprifosbuvir 450 mg. Removal of grazoprevir would eliminate drug–drug interactions caused by the NS3/4A protease inhibitor drug class, and would also eliminate concerns regarding hepatic transaminase elevations with the protease inhibitor, thus potentially enabling use of the two-drug regimen in a broader range of populations. In the C-BREEZE 1 study (NCT02759315), ruzasvir 60 mg and uprifosbuvir 450 mg was well tolerated but demonstrated lower efficacy for those infected with GT3 and GT6 infection compared with those with GT1, GT2, or GT4 infection.¹² It was hypothesized that a higher dose of ruzasvir might improve the efficacy of this regimen and support a pangenotypic profile. In the present study, we evaluated the efficacy, safety, and tolerability of the combination of ruzasvir 180 mg and uprifosbuvir 450 mg in participants with HCV GT1-GT6 infection.

METHODS

Study Design

This was a phase II, nonrandomized, open-label clinical trial (ClinicalTrials.gov identifier, NCT02956629/Merck protocol PN041). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent institutional review boards or ethics committees reviewed and approved the protocol and applicable amendments for each institution, and all participants gave written informed consent. All participants received ruzasvir 180 mg (3 × 60 mg capsules) plus uprifosbuvir 450 mg (3 × 150 mg tablets) orally once daily as separate medications administered under fasting conditions for 12 weeks. Dose modifications were not permitted during the study.

After the first 50 participants of any HCV GT were allocated to treatment, allocation was paused to assess general safety and tolerability at treatment week (TW) 4. When general safety and tolerability were assessed to be acceptable, the subsequent 200 participants were allocated to treatment with an overall stratification based on genotype. The first 50 participants were included in the overall treatment allocation target of the trial.

Participants

Adults aged ≥ 18 years with chronic HCV GT1-6 infection were enrolled. Participants were either treatment-naïve or had experienced virologic failure following treatment with an interferon-containing treatment regimen. Participants with fibrosis stage F0-F4 were eligible; cirrhosis was defined as a liver biopsy study consistent with METAVIR F4, FibroScan[®] performed within 12 months with a result of >12.5 kPa, or a FibroSure[®] (FibroTest[®]) performed during screening with a score of >0.75 and an aspartate aminotransferase (AST) to platelet ratio index (APRI) of >2 . Among those infected with HCV GT1-GT4, the allocation target was 25%-30% individuals with cirrhosis. Participants could also be either HCV-monoinfected or coinfecting with HCV and human immunodeficiency virus (HIV). Participants receiving HIV medications other than tenofovir, abacavir, lamivudine, emtricitabine, raltegravir, dolutegravir, or rilpivirine were excluded.

Participants who had previously received a DAA-based treatment regimen, with hepatitis B virus coinfection (defined as hepatitis B surface antigen-positive), with evidence of decompensated liver disease (presence or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy), with Child-Pugh class B or C cirrhosis (a Child-Pugh-Turcotte score >6), or with evidence of hepatocellular carcinoma were excluded. Participants with alanine aminotransferase (ALT) or AST $>10\times$ upper limit of normal, hemoglobin <10 g/dL, platelets $<50 \times 10^3/\mu\text{L}$, serum albumin <3.0 g/dL, international normalized ratio >1.7 (unless stable on anticoagulant regimen), or estimated glomerular filtration rate <50 mL/min/1.73 m² were also excluded.

End points

The primary efficacy end point was sustained virologic response at 12 weeks after the completion of therapy (SVR12). HCV RNA was assessed using the Roche COBAS[®] AmpliPrep/COBAS[®] TaqMan[®] HCV Test v2.0 with a lower limit of quantitation (LLoQ) <15 IU/mL. Virologic relapse was defined as HCV RNA $\geq$ LLoQ following completion of all study therapy, after becoming undetectable at end of treatment. Secondary end points included the proportion of participants with virologic failure.

Safety and tolerability were assessed through the clinical evaluation of adverse events (AEs), vital signs, physical examinations, electrocardiograms, and standard laboratory safety tests.

Resistance analyses were conducted in all participants with available sequencing data and a treatment outcome of SVR12 or virologic failure (resistance analysis population; RAP). The prevalence and impact on SVR12 of baseline RASs in the NS5A and NS5B regions were assessed using next-generation sequencing (15% sensitivity threshold). NS5A substitutions at amino acid positions 28, 30, 31, or 93 were assessed in all participants. In addition, NS5A RASs at position 58 were assessed in participants with HCV GT3, GT4, or GT6 infection, and RASs at positions 24 or 62 were assessed in participants with GT3 infection. Regardless of HCV genotype, participants who experienced virologic failure had baseline samples sequenced for NS5A RASs at positions 24, 28, 30, 31, 58, 62, or 93. NS5B substitutions at amino acid positions 159, 239, 282, 316, 320, or 321 were also assessed for all genotypes.

Statistics

Planned enrollment was approximately 250 participants, with an allocation target of 50 participants with HCV GT1 infection, 50 with GT2 infection, 50 with GT3 infection, 50 with GT4 infection, and 25 each with GT5 and GT6 infection. The sample size was based on practical considerations that enabled a reasonable estimation of the SVR12 for each genotype. The full analysis set (FAS) population included all participants who received at least one dose of study drug; in this study, the safety population is identical to the FAS. The per-protocol (PP) population excluded participants who discontinued treatment for administrative reasons (lost to follow-up, withdrew consent). However, participants who discontinued treatment because of drug-related AEs were included in the PP population and counted as treatment failures, and any participant categorized as a reinfection was considered a success in the PP population. The RAP excluded participants who discontinued for reasons other than virologic failure.

Results

In total, 329 people were screened, and 282 participants were enrolled between November 2016 and June 2017. Most participants were male (55.3%); median age was 51.0 years; 78.4% were

white; 27.7% had HCV GT1 infection (GT1a, n=46; GT1b, n=30; GT1-other, n=2); 21.6% (n=61) had GT3 infection; 73.0% had baseline HCV RNA >800,000 IU/mL; 20.6% were cirrhotic; 84.0% were treatment-naïve; and 3.9% were HCV/HIV co-infected (**Table 1**). Nearly all participants (273/282, 96.8%) received at least one dose of study medication and completed the follow-up week (FW) 12 visit (**Figure 1**).

SVR

The SVR12 rate was 89.7% (n/N=253/282; 95% confidence interval [CI], 85.6%-93.0%) in the FAS population. Twenty-nine participants did not achieve SVR12; of these, 19 experienced virologic relapse, 2 experienced drug-related AEs, 1 had reinfection, and 7 participants discontinued for non-study medication-related reasons. In the PP population, the SVR12 was 92.3% (251/272; 88.4%-95.2%) (**Table 2**).

The SVR12 rate in participants with HCV GT1a infection was 89.6% (43/48; 95% CI 77.3%-96.5%) (**Table 2**). Of the five participants with GT1a infection who failed to achieve SVR12, two discontinued from the trial (one participant withdrew from study medication prior to TW2 owing to an AE of substance abuse, and one participant withdrew from the trial prior to TW4) and three relapsed. Of those who relapsed, two relapsed at FW4 and one relapsed at FW12 with GT11 that was categorized as GT1a for the analysis. SVR12 appeared to be unaffected by cirrhosis status, with SVR12 rates of 88.9% (8/9) and 97.1% (33/34) in cirrhotic and non-cirrhotic participants, respectively (**Table 3**; FAS population is summarized in **Supplementary Table 1**). SVR12 in participants infected with GT1b infection was 96.7% (29/30; 81.8%-99.9%) (**Table 2**). The only participant with GT1b infection who failed to achieve SVR12 was lost to follow-up at FW4. SVR12 was unaffected by cirrhosis status: 100% (7/7) in cirrhotic participants and 100.0% (22/22) in non-cirrhotic participants, although the number of cirrhotic participants was low (**Table 3**; **Supplementary Table 1**).

SVR12 was 91.5% (43/47; 95% CI, 79.6%-97.6 %) in participants with HCV GT2 infection (**Table 2**). Among the four participants with GT2 who failed to achieve SVR12, one experienced virologic relapse at FW8. The site reported significant non-compliance with study medication dosing for this participant, who took each dose of medication with food and had confirmed low drug exposure. The other three participants who failed to achieve SVR12 all discontinued from the trial: one discontinued owing to drug-related AEs of insomnia and fatigue

prior to TW6, and two were lost to follow-up after FW8. SVR12 was 100% (10/10) in cirrhotic participants and 94.1% (32/34) in non-cirrhotic participants, and was unaffected by baseline HCV RNA (94.1% [16/17] in those with baseline HCV RNA $\leq 2,000,000$ IU/mL and 96.3% [26/27] in those with baseline HCV RNA $> 2,000,000$ IU/mL) (**Table 3; Supplementary Table 1**).

SVR12 rates were the lowest in participants with HCV GT3 infection (73.8%; 45/61; 95% CI 60.9%-84.2%) (**Table 2**). Of the 16 participants with GT3 infection who failed to achieve SVR12, 1 had evidence of reinfection at FW8 (GT3 at baseline and GT1a at FW8), 1 discontinued from the trial owing to a non-drug-related AE of substance abuse prior to TW4, and 14 relapsed (12 by FW4 and 2 by FW8). SVR12 was 68.4% (13/19) in cirrhotic participants with HCV GT3 infection and 80.0% (32/40) in non-cirrhotic participants, and was 91.3% (21/23) in those with baseline HCV RNA $\leq 2,000,000$ IU/mL and 66.7% (24/36) in those with baseline HCV RNA $> 2,000,000$ IU/mL (**Table 3; Supplementary Table 1**).

The SVR12 rate was 98.2% (55/56; 95% CI, 90.4%-100.0%) in participants with HCV GT4 (**Table 2**). The one participant with HCV GT4 infection who failed to achieve SVR12 discontinued study medication owing to a non-drug-related AE of abdominal pain prior to TW6. In the PP population, the SVR12 rate was 100% regardless of cirrhosis status or baseline HCV RNA (**Table 3; Supplementary Table 1**).

SVR12 was 100% in participants with HCV GT5 infection (18/18; 95% CI, 84.7%-100.0%) and 90.9% (20/22; 95% CI, 70.8%-98.9%) in those with GT6 infection (**Table 2**). Two participants infected with HCV GT6 failed to achieve SVR12: one relapsed at FW4 and the other discontinued study medication prior to Day 7 because of the drug-related AEs of anxiety and nausea. In participants with GT6 infection, the SVR12 rate was 100% (4/4) in those with cirrhosis and 88.9% (16/18; 65.3%-98.6%) in those without cirrhosis, and 88.9% (8/9) in participants with baseline HCV RNA $\leq 2,000,000$ IU/mL and 92.3% (12/13) in those with baseline HCV RNA $< 2,000,000$ IU/mL (**Table 3; Supplementary Table 1**).

Compared with SVR12 data for the FAS population, two participants (both with GT6 infection) relapsed between FW12 and FW24.

Efficacy by baseline NS5A RASs

The prevalence of baseline NS5A RASs varied according to HCV genotype, ranging from 0.0% among those infected with HCV GT5 to 86.4% among those infected with HCV GT2, where the majority of these (32/38) were 31L/M (**Supplementary Table 2**). Among those with GT1a infection, the presence of NS5A RAS impacted efficacy (84.6% [11/13] vs 100.0% [31/31] in those with and without RASs, respectively). (**Figure 2**) When efficacy was evaluated according to RAS position, lower efficacy was observed only in the two participants with GT1a infection who had Y93 baseline RAS; one participant had a single Y93 substitution at baseline and the other had substitutions at Y93 and Q30L.

Efficacy for participants with GT1b (n=29) and GT4 (n=54) was not impacted by the presence of NS5A RASs; SVR12 was 100.0% regardless of the presence of RASs (**Figure 2**). Similarly, detectable NS5A RASs did not significantly impact efficacy in those with HCV GT2 infection (SVR12 rates were 97.4% [37/38] and 100.0% [6/6] for those with and without RASs, respectively) (**Figure 2**); the one participant who relapsed had baseline NS5A 31M RAS.

SVR12 rates were lower in participants with HCV GT3 infection and NS5A RASs at baseline compared with those with no RASs at baseline (70% [21/30] vs 86.2% [25/29]) (**Figure 2**). The lower efficacy in GT3-infected participants with baseline RASs was not clearly associated with any specific RAS (**Figure 3**).

All 18 participants with HCV GT5 infection achieved SVR12 (100%; 18/18); none of these participants had detectable NS5A RASs (**Figure 2**). Finally, the rate of SVR12 was 90.9% (10/11) for those with GT6 infection without detectable NS5A RASs and 100.0% (9/9) for those with detectable substitutions (**Figure 2**).

Efficacy by baseline NS5B RASs

The prevalence of baseline NS5B RASs varied among persons in the RAP depending on HCV genotype, ranging from 0.0% among those infected with HCV GT1a, GT3, GT5, or GT6 to 24.1% among those infected with GT1b (**Supplementary Table 2**). There was no impact of baseline NS5B RAS on efficacy across genotypes. All participants with baseline NS5B RASs

achieved SVR12 (9/9; 100%) compared with 92.9% (234/252) of participants without baseline NS5B RASs.

Treatment-emergent RASs

Both of the participants with HCV GT1a infection who relapsed had RASs in the NS5A gene region at baseline; one had substitutions at Y93C, and one at Q30L, H58L, and Y93H. The participant with baseline Y93C had two treatment-emergent substitutions: L31V and Y93H. The other participant had two additional substitutions at failure: the addition of L31V and the further diversity of position 58 (52% L, 46% P). The participant with GT1l infection who relapsed had a baseline R30Q RAS, and an additional treatment-emergent Y93H at failure. The one participant with GT2 infection who experienced virologic failure had a baseline RAS in the NS5A gene region at T24A and L31M, and no substitutions in the NS5B gene region. These substitutions were also present at failure, and no treatment-emergent RASs were detected. The one participant with HCV GT6e infection who relapsed at FW4 did not have detectable baseline RAS; but had treatment-emergent L31M and T93S at the time of relapse. Among the two other participants with GT6 infection who relapsed at FW24, one was GT6q and one was GT6e; neither had any RASs at NS5A or NS5B at baseline or at the time of relapse.

Fourteen participants infected with HCV GT3 had a virologic relapse; 11/14 relapsed by FW4, 2/14 by FW8, and 1 at FW12. Four participants did not have RASs at baseline but had treatment-emergent Y93H at relapse; one of the four also had treatment-emergent S62T. Eight participants had RASs at position S62 at baseline (S62T, n=5; S62M, n=1; S62V, n=1; S62I, n=1); the participant with S62I also had A30S and Y93H at baseline, and one participant with S62T also had a Y93H at baseline. All five participants with S62T at baseline also had S62T at relapse; 3/5 also had treatment-emergent Y93H at relapse, 1/5 had Y93H at baseline and relapse, and 1/5 had treatment-emergent L31F RAS. The participant with A30S, S62I, and Y93H at baseline had the same RASs at relapse. The participant with an S62M RAS at baseline had treatment-emergent S62V/Y93H at relapse, and the participant with S62V at baseline had S62V/Y93H RASs at relapse. The two other participants with GT3 infection who relapsed had A30M/A30K/Y93H and A30K at baseline, and A30K/Y93H and A30K/L31V at relapse (both at FW4).

Treatment-emergent NS5B RASs were observed in one participant with HCV GT3 infection. This participant did not have any NS5A or NS5B RASs detected at baseline, and experienced virologic failure at FW8 with treatment-emergent Y93H in the *NS5A* gene region and S282T RAS in the *NS5B* gene region; however, no NS5B RASs were detected in this region at FW12 and FW24.

Safety

The majority of participants reported at least one AE (173/282; 61.3%); the most common AEs (reported in $\geq 5\%$) were headache (n=33, 11.7%), fatigue (n=29, 10.3%), nausea (n=19, 6.7%), and diarrhea (n=14, 5.0%). Drug-related AEs were reported by 94 participants (33.3%); the most common were fatigue (n=22, 7.8%) and headache (n=21, 7.4%). Seven (2.5%) participants reported 12 serious AEs during the trial (1 each of acute coronary syndrome, diarrhea, abscess limb, cellulitis, sinusitis, fall, rhabdomyolysis, acute kidney injury, increased ammonia level, increased blood creatinine level, decreased glomerular filtration rate, and ovarian cyst), none of which were assessed to be drug-related. Five participants (1.8%) reported AEs leading to discontinuation of study medication, including substance abuse (n=2), anxiety and nausea (n=1), insomnia and fatigue (n=1), and abdominal pain (n=1); two (0.7%) of these were considered drug-related AEs (anxiety and nausea; insomnia and fatigue).

Two participants experienced hepatic events of clinical interest, defined as the first instance of ALT or AST >500 IU/L, or ALT or AST $>3\times$ nadir and $>3\times$ the upper limit of normal (ULN) from the initiation of study therapy through the first 14 days of follow-up. One participant had an asymptomatic elevation of AST (153 U/L) at TW4 associated with an elevated creatine phosphokinase level. One participant sustained a fall with resultant rhabdomyolysis that was reported as a serious AE not related to study medication, and the associated elevated ALT met criteria for a hepatic event of clinical interest. This same participant met criteria for a renal event of clinical interest, defined as the first instance of an estimated glomerular filtration rate <50 mL/min/1.73 m² from the initiation of study therapy through 14 days following treatment, or the first instance of serum creatinine grade 2 or higher ($>1.3 \times$ ULN) and elevated from baseline from the initiation of study therapy through 14 days following treatment.

Discussion

The combination of ruzasvir 180 mg and uprifosbuvir 450 mg for 12 weeks was generally well tolerated. High efficacy was observed in participants with HCV GT1, GT2, GT4, GT5, and GT6 infection, with lower efficacy in those with GT3 infection. Although the number of participants was small, the study results suggest a potential impact of baseline NS5A Y93 RAS in persons with GT1a. Efficacy was not affected by cirrhosis status or RASs in those with GT1b, GT2, GT4, and GT5 infection. Efficacy was lower in participants infected with HCV GT3 regardless of cirrhosis status and was only partially accounted for by baseline NS5A RASs.

The C-BREEZE-1 trial of ruzasvir 60 mg plus uprifosbuvir 450 mg did not show pangenotypic activity; SVR12 rates were high among those with HCV GT1a (96%; 52/54), GT1b (100%; 15/15), GT2 (97% 28/29), and GT4 infection (90%; 18/20), with lower efficacy in those with GT3 (77%; 33/39) and GT6 infection (67%; 2/3).¹² In the phase II C-CREST trials, the three-drug regimen of ruzasvir 60 mg and uprifosbuvir 450 mg in combination with grazoprevir 100 mg, with or without ribavirin, resulted in SVR12 rates of >90% in a broad patient population with HCV GT1, GT2, GT3, GT4, or GT6 infection.^{9,10} It was hypothesized that a higher dose of ruzasvir might improve pangenotypic activity of the ruzasvir and uprifosbuvir combination and compensate for the lack of NS3/4A inhibition provided by grazoprevir in the C-CREST trials. In the current trial of uprifosbuvir 450 mg and the higher dose of ruzasvir 180 mg, SVR12 rates in the FAS population were not meaningfully higher than those observed with the lower dose of ruzasvir 60 mg in combination with uprifosbuvir.

In the current trial, we hypothesized that an increased dose of ruzasvir would overcome the lower efficacy in individuals with HCV GT3 infection observed in C-BREEZE-1.¹² However, we observed that the ruzasvir 180 mg dose used in the present study did not result in higher efficacy in participants with GT3 infection compared with the 60-mg dose of ruzasvir used in C-BREEZE-1 (SVR12 rates of 77% and 73.8%, respectively).¹² It is possible that a plateau was reached on the dose-response curve such that increasing the dose of ruzasvir did not result in any increase in efficacy for GT3 infection. The larger number of participants with GT6 infection who were enrolled in C-BREEZE-2 enabled us to more thoroughly evaluate efficacy in this population compared with C-BREEZE-1 (90.9% [20/22] vs 67% [2/3]). Although there was no appreciable difference in SVR12 rates between the lower and the higher ruzasvir doses used

in C-BREEZE-1 and C-BREEZE-2, a difference was seen between the ruzasvir plus uprifosbuvir two-drug combination regimen and the ruzasvir-uprifosbuvir-grazoprevir triple-drug regimen evaluated in the C-CREST studies,⁹⁻¹¹ suggesting that for the particular combination of ruzasvir and uprifosbuvir, a third drug is required to ensure a pangenotypic profile. A three-drug combination including uprifosbuvir, grazoprevir, and ruzasvir at the higher dose of 180 mg of ruzasvir has not been evaluated.

In the C-BREEZE-1 trial, lower efficacy was observed in cirrhotic participants; 10 of 13 participants who relapsed had cirrhosis, including 6 of 9 participants with HCV GT3 infection (67%).¹² Coupled with an analysis of RASs, the data from C-BREEZE-1 suggested that infection with HCV GT1a, GT3, or GT6 in participants who were cirrhotic and/or had baseline RASs was associated with lower SVR rates after treatment with ruzasvir 60 mg plus uprifosbuvir 450 mg.¹² In the current analysis, SVR12 rates in the GT3 subtype were 68.4% (13/19) in cirrhotic participants and 80.0% (32/40) in noncirrhotic participants (PP population). However, 57.1% (8/14) of GT3-infected participants in the PP population with virologic failure were noncirrhotic, suggesting that cirrhosis status may not have as clinically relevant an impact on SVR12 as previously hypothesized.

Historically, the presence of RASs at baseline has been associated with lower SVR12 rates with some DAA regimens. In our trial, all three participants with HCV GT1 infection who experienced virologic failure (GT1a, n=2; GT11, n=1) had baseline RASs (Y93C, Q30L/ Y93H, and R30Q, respectively). Participants with HCV GT3 infection who experienced virologic failure were likely to have NS5A RASs at baseline (71.4%; 10/14) and at relapse (100%; 14/14), which is in contrast to the results of the C-BREEZE-1 trial, where two of nine participants with GT3 infection who relapsed had baseline NS5A RASs.¹² The most common baseline NS5A RAS in GT3-infected participants was at S62 (57.1%; 8/14), and the most common treatment-emergent RAS was Y93H (71.4% 10/14). The presence of Y93H at baseline has previously been shown to impact the efficacy of DAAs, while the double RAS combinations A30K + L31M and A30K + Y93H and the triple combination A30K + L31M + Y93H have been shown to severely impact susceptibility to daclatasvir, velpatasvir, and elbasvir and to modestly impact susceptibility to pibrentasvir.¹³ It has also been shown that S62 substitutions, while not directly impacting the SVR rate achieved with daclatasvir, may modify the effects of other RASs.¹⁴ Of

note, 75% (6/8) of HCV GT3–infected participants with baseline S62 RASs had treatment-emergent RASs: five had treatment-emergent Y93H and one had treatment-emergent L31F. While single S62 substitutions cause minimal (0.2 to 20-fold) shifts in the ruzasvir EC₅₀ in vitro, the presence of additional RASs on the same genome can result in substantial potency losses. The combination of S62I/L/T and Y93H in the GT3 replicon conferred potency losses >1000-fold to ruzasvir. Thus, selection of the treatment-emergent RASs in addition to the baseline S62 substitutions impacted ruzasvir potency in those virologic failures.

Interpretation of this analysis is subject to several limitations. The size of each genotype population was small, limiting the precision of efficacy measures. This is particularly notable for subpopulations with baseline RASs. The study also had limited enrollment of potentially important subpopulations, such as black participants and those co-infected with HCV/HIV. Finally, there was no direct comparison to either standard-of-care DAA regimens nor to ruzasvir 60 mg plus uprifosbuvir 450 mg in the same trial.

In conclusion, data from the present study indicate that the combination of ruzasvir 180 mg plus uprifosbuvir 450 mg once daily for 12 weeks was well tolerated overall but was suboptimal as a pangenotypic regimen.

Statement of Interests

Conflict of Interests: This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD).

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425 The following authors have nothing to disclose: Mordechai Rabinovitz, Eduard Z. Burnevich,
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428 **Author Contributions**

429 Eric Lawitz contributed to the acquisition of the data, interpretation of the results, and critically
430 reviewing and revising the manuscript for important intellectual content. Edward Gane
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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

TABLE 1 Baseline patient demographics.

Characteristic	HCV genotype						All participants N=282
	GT1 n=78	GT2 n=47	GT3 n=61	GT4 n=56	GT5 n=18	GT6 n=22	
Sex, n (%)							
Male	43 (55.1)	23 (48.9)	34 (55.7)	33 (58.9)	7 (38.9)	16 (72.7)	156 (55.3)
Female	35 (44.9)	24 (51.1)	27 (44.3)	23 (41.1)	11 (61.1)	6 (27.3)	126 (44.7)
Age, median (range), years	49.5 (19-69)	54.0 (27- 73)	51.0 (26-67)	48.0 (23- 81)	57.5 (29-74)	57.5 (33- 69)	51.0 (19-81)
Race, n (%)							
Asian	2 (2.6)	2 (4.3)	2 (3.3)	0 (0)	1 (5.6)	22 (100.0)	29 (10.3)
Black	4 (5.1)	0 (0)	1 (1.6)	8 (14.3)	9 (50.0)	0 (0)	22 (7.8)
Multiple	1 (1.3)	0 (0)	1 (1.6)	0 (0)	4 (22.2)	0 (0)	6 (2.1)
Native Hawaiian or other Pacific Islander	2 (2.6)	1 (2.1)	0 (0)	1 (1.8)	0 (0)	0 (0)	4 (1.4)
White	69 (88.5)	44 (93.6)	57 (93.4)	47 (83.9)	4 (22.2)	0 (0)	221 (78.4)
Ethnicity, n (%)							
Hispanic/Latino	13 (16.7)	14 (29.8)	12 (19.7)	0 (0)	0 (0)	0 (0)	39 (13.8)

Not Hispanic or Latino	64 (82.1)	32 (68.1)	49 (80.3)	54 (96.4)	18 (100.0)	22 (100.0)	239 (84.8)
Not reported	1 (1.3)	1 (2.1)	0 (0)	2 (3.6)	0 (0)	0 (0)	4 (1.4)
Body-mass index							
kg/m ² , median (range)	26.8 (14.2-42.6)	27.5 (18.9-50.4)	27.4 (17.1-41.6)	25.3 (18.9-35.7)	30.2 (17.3-40.3)	24.8 (17.3-30.1)	26.8 (14.2-50.4)
≥30 kg/m ² , n (%)	22 (28.2)	14 (29.8)	18 (29.5)	11 (19.6)	9 (50.0)	1 (4.5)	75 (26.6)
Baseline HCV RNA, n (%)							
>800,000 IU/mL	59 (75.6)	34 (72.3)	45 (73.8)	39 (69.6)	14 (77.8)	15 (68.2)	206 (73.0)
>2,000,000 IU/mL	44 (56.4)	29 (61.7)	36 (59.0)	24 (42.9)	11 (61.1)	13 (59.1)	157 (55.7)
Cirrhosis, n (%)	17 (21.8)	10 (21.3)	20 (32.8)	6 (10.7)	1 (5.6)	4 (18.2)	58 (20.6)
HCV/HIV co-infected, n (%)	4 (5.1)	1 (2.1)	0 (0)	6 (10.7)	0 (0)	0 (0)	11 (3.9)
Treatment history, n (%)							
Treatment-naive	67 (85.9)	45 (95.7)	52 (85.2)	42 (75.0)	14 (77.8)	17 (77.3)	237 (84.0)
Treatment-experienced	11 (14.1)	2 (4.3)	9 (14.8)	14 (25.0)	4 (22.2)	5 (22.7)	45 (16.0)
<i>IL28B</i> genotype, n (%)							
CC	23 (29.5)	23 (48.9)	24 (39.3)	17 (30.4)	1 (5.6)	16 (72.7)	104 (36.9)
Non-CC	53	24 (51.1)	35	39 (69.6)	17	6 (27.3)	174 (61.7)

	(67.9)		(57.4)		(94.4)		
Unknown	2 (2.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.4)

GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.

TABLE 2 SVR12 in the full analysis set population and the per protocol population.

	HCV genotype							All participants
	GT1a	GT1b	GT2	GT3	GT4	GT5	GT6	
Full analysis set	n=48	n=30	n=47	n=61	n=56	n=18	n=22	N=282
SVR, n/N (%)	43/48 (89.6%)	29/30 (96.7%)	43/47 (91.5%)	45/61 (73.8%)	55/56 (98.2%)	18/18 (100%)	20/22 (90.9%)	253/282 (89.7%)
Non-SVR, n	5	1	4	16	1	0	2	29
Relapse	3	0	1	14	0	0	1	19
Reinfection	0	0	0	1 ^a	0	0	0	1
AE	1	0	0	1	1	0	0	3
DRAE	0	0	1	0	0	0	1	2
LTFU/withdrawn	1	1	2	0	0	0	0	4
Per-protocol analysis	n=45	n=29	n=44	n=59	n=55	n=18	n=22	N=272
Excluded from PP, n	3	1	3	2	1	0	0	10
SVR ^{b,c,d}	1 ^b	0	1 ^c	1 ^d	0	0	0	3
Non-SVR	2	0	2	1	1	0	0	7
AE	1	0	0	1	1	0	0	3
LTFU/withdrawn	1	1	2	0	0	0	0	4
SVR, n/N (%)	42/45 (93.3%)	29/29 (100%)	42/44 (95.5%)	45/59 (76.3%) ^a	55/55 (100%)	18/18 (100%)	20/22 (90.9%)	251/272 (92.3%)
Non-SVR, n	3	0	2	14	0	0	2	21

Relapse	3	0	1	14	0	0	1	19
DRAE	0	0	1	0	0	0	1	2

AE, adverse event. DRAE, drug-related adverse event; GT, genotype; HCV, hepatitis C virus; LTFU, lost to follow-up; PP, per-protocol; SVR, sustained virologic response.

^aOne participant with HCV GT3 infection had evidence of reinfection during follow-up (GT3 at baseline, GT1a at follow-up week 8). This participant was considered as non-SVR within the full analysis set (FAS) analysis but was considered as achieving SVR within the PP analysis.

^bOne participant with HCV GT1a infection withdrew during treatment but continued in the study and had plasma collection 12 weeks after treatment discontinuation; this participant was considered as achieving SVR within the FAS analysis but was excluded from the PP analysis owing to withdrawal from study.

^cOne participant with HCV GT2 infection withdrew during treatment but continued in the study and had plasma collection 12 weeks after treatment discontinuation; this participant was considered as achieving SVR within the FAS analysis but was excluded from the PP analysis due to withdrawal from study.

^dOne participant with HCVGT3 infection withdrew during treatment but continued in the study and had plasma collection 12 weeks after treatment discontinuation; this participant was considered as achieving SVR within the FAS analysis but was excluded from the PP analysis owing to physician decision.

TABLE 3 SVR12 in select subgroups (per-protocol population).

	HCV genotype	
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	GT1a n=45	GT1b n=29	GT2 n=44	GT3 n=59	GT4 n=55	GT5 n=18	GT6 n=22	All participants N=272
Race, % (n/N)								
White	95.0 (38/40)	100.0 (26/26)	97.6 (40/41)	78.2 (43/55)	100.0 (46/46)	100.0 (4/4)	0	92.9 (197/212)
Black	50.0 (1/2)	100.0 (1/1)	0	0 (0/1)	100.0 (8/8)	100.0 (9/9)	0	90.5 (19/21)
Asian	0	100.0 (2/2)	100.0 (2/2)	50.0 (1/2)	0	100.0 (1/1)	90.9 (20/22)	89.7 (26/29)
Native Hawaiian or other Pacific Islander	100.0 (2/2)	0	0 (0/1)	0	100.0 (1/1)	0	0	75.0 (3/4)
Multiple	100.0 (1/1)	0	0	100.0 (1/1)	0	100.0 (4/4)	0	100.0 (6/6)
Cirrhosis status, % (n/N)								
Cirrhotic	88.9 (8/9)	100.0 (7/7)	100.0 (10/10)	68.4 (13/19)	100.0 (6/6)	100.0 (1/1)	100.0 (4/4)	87.5 (49/56)
Non-cirrhotic	97.1 (33/34)	100.0 (22/22)	94.1 (32/34)	80.0 (32/40)	100.0 (49/49)	100.0 (17/17)	88.9 (16/18)	93.5 (202/216)
Baseline HCV RNA, % (n/N)								

≤800,000 IU/mL	100.0 (10/10)	100.0 (7/7)	91.7 (11/12)	100.0 (15/15)	100.0 (16/16)	100.0 (4/4)	85.7 (6/7)	97.2 (70/72)
>800,000 IU/mL	91.4 (32/35)	100.0 (22/22)	96.9 (31/32)	68.2 (30/44)	100.0 (39/39)	100.0 (14/14)	93.3 (14/15)	90.5 (181/200)
≤2,000,000 IU/mL	100.0 (17/17)	100.0 (13/13)	94.1 (16/17)	91.3 (21/23)	100.0 (31/31)	100.0 (7/7)	88.9 (8/9)	96.6 (115/119)
>2,000,000 IU/mL	89.3 (25/28)	100.0 (16/16)	96.3 (26/27)	66.7 (24/36)	100.0 (24/24)	100.0 (11/11)	92.3 (12/13)	88.9 (136/153)

GT, genotype; HCV, hepatitis C virus.

FIGURE 1 Participant disposition by HCV genotype for SVR12.

AE, adverse event; GT, genotype; HCV, hepatitis C virus; LTFU, lost to follow-up; SVR12, sustained virologic response 12 weeks after end of treatment.

^aIncludes all participants who received at least one dose of study medication.

^bIncludes two individuals with HCV GT1-other infection.

FIGURE 2 SVR12 by HCV genotype and presence of baseline NS5A resistance-associated substitutions. Pie charts indicate prevalence of baseline RASs. NS5A substitutions at amino acid positions 28, 30, 31, and 93 were evaluated for all participants with HCV GT1-GT6 infection). In participants with GT3, GT4, GT5, and GT6 infection, NS5A substitutions at position 58 were also evaluated, and additionally, in participants with GT3 infection, substitutions at position 62 were evaluated.

GT, genotype; HCV, hepatitis C virus; NS5A, nonstructural protein 5 A; RAS, resistance-associated substitution; SVR12, sustained virologic response at 12 weeks after completion of therapy.

^aIncludes two participants with HCV GT1-other infection.

FIGURE 3. SVR12 by HCV GT3 genotype and RAS. GT, genotype; HCV, hepatitis C virus; RAS, resistance-associated substitution; SVR12, sustained virologic response at 12 weeks after completion of therapy.

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