Safety and efficacy of a fixed-dose combination regimen of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin in participants with and without cirrhosis with chronic hepatitis C virus genotype 1, 2, or 3 infection (C-CREST-1 and C-CREST-2, part B): two randomised, phase 2, open-label trials

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Summary

Background There is a need for hepatitis C virus (HCV) therapies with excellent efficacy across genotypes and in diverse populations. Part A of the C-CREST-1 and C-CREST-2 trials led to the selection of a three-drug regimen of grazoprevir (MK-5172; an HCV NS3/4A protease inhibitor; 100 mg/day) plus ruzasvir (MK-8408; an NS5A inhibitor; 60 mg/day) plus uprifosbuvir (MK-3682; an HCV NS5B polymerase inhibitor; 450 mg/day). Part B of the studies tested this combination as a single formulation in different treatment durations in a broader population.

Methods Part B of these randomised, phase 2, open-label clinical trials enrolled individuals from 15 countries who were chronically infected with HCV genotypes 1–6 (HCV RNA ≥10 000 IU/mL) with or without compensated cirrhosis. Those with genotype 1, genotype 2, genotype 4, or genotype 6 were treatment-naive; those with genotype 3 could be treatment-naive or treatment-experienced with pegylated interferon and ribavirin. Randomisation occurred centrally using an interactive voice response system and integrated web response system. Participants were randomly assigned to receive treatment for 8, 12, or 16 weeks with a fixed-dose combination of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin. The primary endpoint was the proportion of participants achieving sustained virological response 12 weeks after the end of all study therapy (SVR12), defined as HCV RNA less than the lower limit of quantification (either target detected unquantifiable or target not detected [<15 IU/mL]). The trials are registered at ClinicalTrials.gov, numbers NCT02332707 and NCT02332720.

Findings 676 participants were randomly assigned between Feb 18, 2015, and Aug 16, 2016. In all 675 participants who received at least one dose of study drug (full analysis set), SVR12 for the 8-week regimen of grazoprevir, ruzasvir, and uprifosbuvir with and without ribavirin was achieved in 39 (93% [95% CI 81–99]) of 42 participants with genotype 1a, 45 (98% [88–100]) of 46 with genotype 1b, 54 (86% [75–93]) of 63 with genotype 2, 98 (95% [89–98]) of 103 with genotype 3, and seven (100% [59–100]) of seven participants with genotype 4. SVR12 for the 12-week regimen with and without ribavirin was achieved in 87 (99% [95% CI 94–100]) of 88 participants with genotype 1, 61 (98% [91–100]) of 62 with genotype 2, and four (100% [40–100]) of four with genotype 6. Among participants with cirrhosis who were infected with genotype 3, SVR12 for the 12-week regimen with and without ribavirin was achieved in 28 (97% [95% CI 82–100]) of 29 of those who were treatment-naive and 29 (100% [88–100]) of 29 who were treatment-experienced. SVR12 for the 16-week regimen with and without ribavirin was achieved in 26 (100% [95% CI 87–100]) of 26 participants with genotype 2 infection and 72 (96% [89–99]) of 75 participants with genotype 3 infection. The most common adverse events were headache (143 [22%] of 664), fatigue (129 [19%] of 664), and nausea (83 [13%] of 664). 16 (2%) of 664 participants had serious adverse events.

Interpretation The combined regimen of grazoprevir (100 mg/day), ruzasvir (60 mg/day), and uprifosbuvir (450 mg/day) has the potential to provide a simplified treatment for HCV that is effective and well tolerated in most individuals infected with HCV, as well as a shorter duration of treatment in many individuals.

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Introduction

An estimated 70–180 million people worldwide and 3·5 million people in the USA are chronically infected with hepatitis C virus (HCV).[1–3] Recent evidence indicates that HCV incidence might be increasing in the USA.[4] Although the number of people infected with HCV in

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Research in context

Evidence before this study

We searched PubMed and meeting abstracts (European Association for the Study of the Liver and American Association for the Study of Liver Diseases) from Jan 1, 2012, to Feb 23, 2017, for clinical trials of participants infected with hepatitis C virus (HCV), with the terms "HCV" and "hepatitis C" without language restrictions. Most currently approved treatments for HCV, with the exception of glecaprevir plus pibrentasvir or sofosbuvir plus velpatasvir, do not have pan-genotypic efficacy. However, the efficacy rate after 12 weeks of treatment with sofosbuvir plus velpatasvir among participants infected with genotype 3 with cirrhosis who had received previous treatment with pegylated interferon and ribavirin was lower, at 89%, compared with other groups. These results show the need for better treatment options for this population. Results with three-drug regimens, such as sofosbuvir plus velpatasvir plus voxilaprevir (a protease inhibitor), have shown efficacy in harder-to-treat populations, such as those who are treatment-experienced, those infected with genotype 3, and those with cirrhosis.

Added value of this study

This study found that an 8-week combination regimen of grazoprevir (100 mg/day), ruzasvir (60 mg/day), and uprifosbuvir (450 mg/day) was highly efficacious in participants chronically infected with HCV genotypes 1, 3, and 4, but less so for genotype 2. The 12-week combination regimen was highly efficacious in those chronically infected with HCV genotypes 1, 2, 3, and 6, and the 16-week combination regimen (not tested in genotypes 1, 4, or 6) in those chronically infected with HCV genotypes 2 and 3. Among treatment-naive and treatment-experienced participants infected with genotype 3, high rates of efficacy were observed after 12 weeks of treatment with this combination regardless of the presence of cirrhosis.

Implications of all the available evidence

The novel three-drug combination of grazoprevir, ruzasvir, and uprifosbuvir has the potential to provide a single, short duration regimen that is safe and effective for the treatment of multiple HCV genotypes. A 12-week regimen with grazoprevir, ruzasvir, and uprifosbuvir without ribavirin was highly effective and well tolerated for the treatment of HCV infection in these phase 2 trials, including in individuals with cirrhosis infected with genotype 3 who had previously received treatment with pegylated interferon and ribavirin.

the USA could decrease over time due to the availability of treatment with oral direct-acting antiviral agents (DAAs), most are unaware of their infection.[5,6] Accessibility to effective, short-course, well tolerated HCV treatments could encourage increased screening for HCV and engagement in care that could lead to higher uptake of treatment resulting in cure.

A need exists for new HCV therapies, especially for those with cirrhosis, those infected with genotype 3, or those who have previously failed treatment, including treatment with DAAs.[7] Combining three potent DAAs, including an HCV NS3/4A protease inhibitor, an HCV NS5A inhibitor, and an HCV NS5B polymerase inhibitor, has the potential to provide excellent efficacy across multiple genotypes and across diverse populations, simplify treatment by shortening treatment durations for certain populations, and eliminate the need for ribavirin.

Part A of C-CREST-1 and C-CREST-2 evaluated 8-week durations of three-drug combinations of grazoprevir (MK-5172; an HCV NS3/4A protease inhibitor) plus either elbasvir (MK-8742; an NS5A inhibitor)[8] or ruzasvir (MK-8408; an NS5A inhibitor)[9] plus either 300 mg/day or 450 mg/day of uprifosbuvir (MK-3682; an HCV NS5B polymerase inhibitor) in people infected with genotype 1, 2, or 3, who were treatment-naive, did not have cirrhosis, and were not co-infected with HIV:[10,11] an 8-week regimen of grazoprevir (100 mg/day) plus ruzasvir (60 mg/day) plus uprifosbuvir (450 mg/day) resulted in sustained virological response at 12 weeks of greater than 90% in participants infected with genotype 1, 2, or 3. The goals of part B of C-CREST-1 and C-CREST-2 were to further evaluate the efficacy, safety, and tolerability of treatment for 8, 12, and 16 weeks with a fixed-dose combination of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin among a broader population of individuals, including those infected with HCV genotypes 1–6, those with cirrhosis, those with HCV–HIV co-infection, and those previously treated with pegylated interferon and ribavirin (genotype 3 only). This Article describes the efficacy and safety results from the completed part B of C-CREST-1 and C-CREST-2 together with the relevant treatment groups from part A, in which participants received the equivalent 8-week regimen of grazoprevir (100 mg/day) plus ruzasvir (60 mg/day) plus uprifosbuvir (450 mg/day), to allow for a more statistically robust analysis.

Methods

Study design and participants

In part A of C-CREST-1 and C-CREST-2, grazoprevir plus ruzasvir plus uprifosbuvir were given as single entities. For part B, the selected regimen of grazoprevir plus ruzasvir plus uprifosbuvir was formulated into a fixed-dose combination tablet and given as two tablets, once daily, without regard to food, for a total daily dose of 100 mg of grazoprevir, 60 mg of ruzasvir, and 450 mg of uprifosbuvir.

Key inclusion criteria were documented chronic HCV genotype 1a, 1b, 2, 3, 4, 5, or 6 infection with HCV RNA of at least 10 000 IU/mL. Individuals with genotype 1, 2, 4, 5, or 6 infection were to be treatment-naive, whereas individuals with genotype 3 were treatment-naive or had previously received treatment with pegylated interferon

and ribavirin. Participants could be HCV mono-infected or HIV–HCV co-infected and could either not have cirrhosis or have compensated cirrhosis as defined by: liver biopsy before day 1 showing cirrhosis (F4); Fibroscan within 12 months, with a result of greater than 12·5 kPa; or a Fibrosure (FibroTest) score of greater than 0·75 and aspartate aminotransferase (AST) to platelet ratio index (APRI) of greater than 2. Those with genotypes 4–6 infection were not eligible if they had cirrhosis. Key exclusion criteria were decompensated liver disease (eg, Child-Pugh class B or C), co-infection with HBV, evidence or suspicion of hepatocellular carcinoma, or protocol-specified substantial laboratory abnormalities. All participants provided written informed consent. The study was done in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice. Independent ethics committees reviewed and approved the protocol and applicable amendments for each institution.

Participants from Canada, Denmark, France, Germany, Israel, Italy, Lithuania, New Zealand, Poland, Spain, Sweden, the UK, and the USA infected with HCV genotype 1 were randomly assigned to either 8 or 12 weeks of grazoprevir, ruzasvir, and uprifosbuvir without ribavirin. Participants infected with HCV genotype 2 were randomly assigned to 8 or 12 weeks of the combined regimen with or without ribavirin, or 16 weeks without ribavirin. Total daily mg doses of ribavirin were based on kg body weight (<66 kg, 800 mg; 66–80 kg, 1000 mg; 81–105 kg, 1200 mg; and >105 kg, 1400 mg) given in divided oral doses in the morning and evening. Participants infected with HCV genotype 3 were randomly assigned to 8, 12, or 16 weeks of the combined regimen with or without ribavirin. Participants infected with genotype 2 or 3 with cirrhosis were randomly assigned only to the 12-week or 16-week treatment duration groups. Those infected with genotype 4 were assigned to treatment for 8 weeks and those with genotype 6 infection were assigned to treatment for 12 weeks. Although this study was open to participants infected with genotype 5, none was enrolled. The target enrolment was between ten and 40 participants per group (appendix pp 4, 7, 8; see protocols in appendix pp 19–364). The sample sizes were selected to provide a reasonable estimate of the SVR12 for each duration, regimen, genotype, and participant population.

Given the scarcity of individuals infected with genotypes 4 and 6 in designated study sites, there was a delay in their recruitment. As such, only preliminary safety and efficacy results for these participants are summarised here since final data are not yet available. This Article presents the final results for 664 participants infected with genotypes 1–3 and preliminary results for 11 participants infected with genotypes 4–6.

Randomisation and masking

The study was a randomised, open-label trial with part A enrolled first followed by part B. Part B enrolled all groups concurrently. Randomisation occurred centrally using an interactive voice response system and integrated web response system. A computer-generated randomisation schedule was produced to define which individuals were to be assigned to each group. At the time the randomisation schedule was generated, component identification schedules were also produced to facilitate the correct distribution of treatments. The open-label drug supplies were labelled with component identification numbers. The randomisation schedule and component identification schedules were loaded into the interactive voice response system and integrated web response system. After an individual met all study criteria and was ready to receive the first dose of study medication on day 1, study sites contacted the interactive voice response system and integrated web response system for assignment of the drug regimen to be given, including component identification and duration of treatment. Within each genotype and cirrhotic status, participants were randomly assigned with stratification for HIV co-infection status. Details on the randomisation scheme are shown in the appendix (pp 7, 8).

Procedures

HCV RNA concentrations in plasma were measured using the Roche COBAS AmpliPrep/COBAS TaqMan HCV Test, version 2.0 (Roche Diagnostics, Basel, Switzerland). Specimens for viral load measurements were collected at screening; treatment days 1, 3, and 7; treatment weeks 2, 3, 4, 6, 8, and when applicable at treatment weeks 10, 12, 14, and 16; and follow-up weeks 2, 4, 8, 12, and 24.

The presence of viruses with resistance-associated substitutions (RASs) in NS3, NS5A, and NS5B was detected by next-generation sequencing (NGS) with a 15% sensitivity threshold (MiSeq, Illumina Inc, San Diego, CA, USA) at baseline (day 1) and at virological failure, if applicable. Sequences were aligned to genotype-specific reference sequences as follows: genotype 1a, H77 (NC_004102); genotype 1b, Con1 (AJ238799); genotype 2, JFH-1 (AB047639); and genotype 3, S52 (GU814263). The specific NS5A loci evaluated were 28, 30, 31, and 93 in genotype 1; 24, 28, 30, 31, 32, 38, 58, 92, and 93 in genotype 2; and 24, 28, 30, 31, 32, 38, 58, 62, 92, and 93 in genotype 3. The NS3 loci evaluated were 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175. The NS5B loci evaluated were 159, 239, 282, 316, 320, and 321.

See Online for appendix

Grazoprevir-related late on-treatment aminotransferase (alanine aminotransferase [ALT] or AST or both) elevation events were defined as ALT or AST or both elevated to greater than five times the upper limit of normal (ULN) occurring after treatment week 4 in those who had normalisation of ALT or AST (≤ULN) between treatments weeks 2 and 4.

Outcomes

The primary endpoint was the proportion of participants achieving sustained virological response 12 weeks after the end of all study therapy (SVR12), defined as HCV RNA less

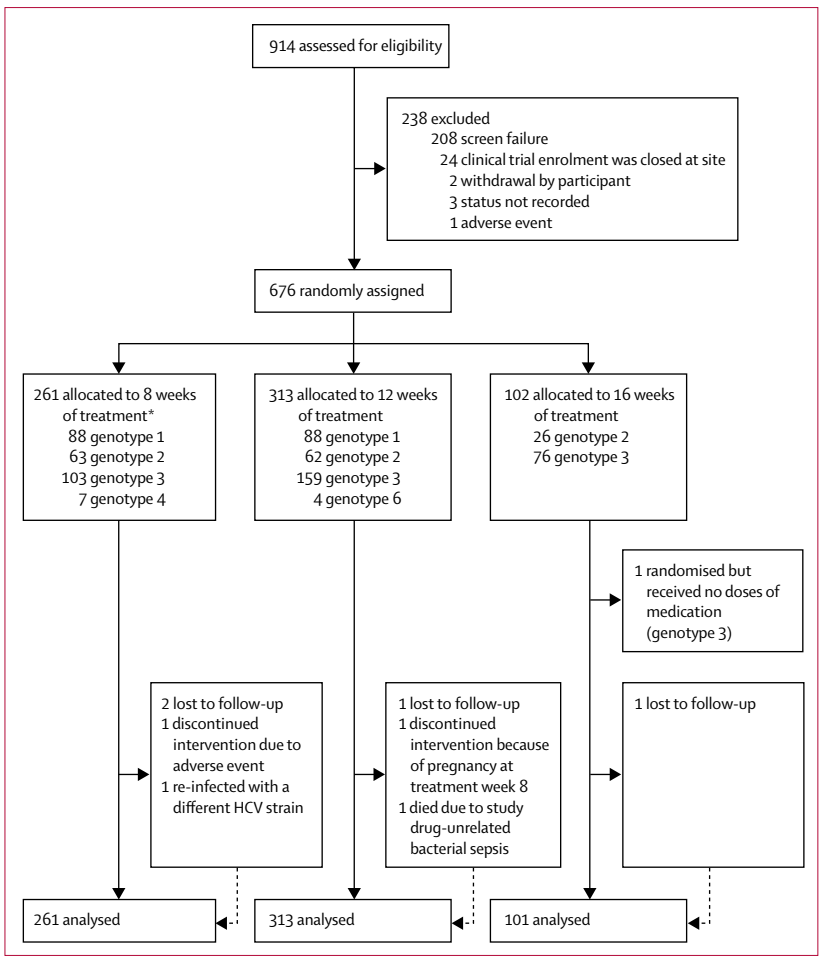

Figure 1: **Trial profile (full analysis set)**
HCV=hepatitis C virus. *Includes 61 participants from part A.

than the lower limit of quantification (either target detected unquantifiable or target not detected [<15 IU/mL]). Virological failures included relapse, non-response, rebound, and virological breakthrough. Relapse was defined as an HCV RNA of at least 15 IU/mL following the end of all study therapy after achieving HCV RNA of less than the lower limit of quantification at the end of treatment, confirmed with a separate blood draw repeated within 2 weeks; non-response was defined as HCV RNA detected at end of all study therapy without achieving undetectable while on treatment; rebound was defined as a greater than 1 $\log_{10}$ IU/mL increase in HCV RNA from the lowest level of HCV RNA while on treatment, confirmed with a separate blood draw within 2 weeks; breakthrough was defined as HCV RNA greater than the lower limit of quantification (15 IU/mL) after being less than the lower limit of quantification previously while on treatment, confirmed with an HCV RNA of at least 15 IU/mL from a separate blood draw repeated within 2 weeks.

Secondary outcomes included the evaluation of the proportion of participants achieving SVR24 (HCV RNA less than the lower limit of quantification at 24 weeks after the end of all study therapy, the evaluation of the proportion of HIV-1 co-infected participants who developed HIV-1 virological failure (HIV-1 RNA >200 copies per mL), and the effect of the study regimens on CD4+ T-cell counts in HIV-1 co-infected participants. The HIV-1-related endpoints will be reported elsewhere. Exploratory outcomes included the viral kinetics in each arm of the study and their relationship to SVR12, and the emergence of viral RASs. Exploratory outcomes that will be reported elsewhere include the evaluation of the pharmacokinetics of the study drugs, and the relationship between human genetic variations and responses to the treatments administered.

Statistical analysis

The primary efficacy objective of this study was to estimate the SVR12 for each treatment group, which was estimated with a two-sided 95% CI (using the Clopper-Pearson method[12]) constructed for each treatment group or combinations of treatment groups defined by cirrhosis status, genotype, treatment duration, or presence of ribavirin in the regimen using SAS version 9.3. The analysis populations (see below) determined the denominator used for estimating the SVR12. The primary endpoint SVR12 for each of the treatment groups is presented in the appendix (pp 9–10). A secondary objective of this study was to estimate the SVR24 and a two-sided 95% CI for each treatment group separately. Those lost to follow-up before follow-up week 24 for reasons unrelated to treatment were imputed as failures.

For the 8-week treatment durations of grazoprevir plus ruzasvir plus uprifosbuvir 450 mg, the efficacy results for part A (single entities) alone and part B (fixed-dose combination) alone are presented separately in the appendix (p 11). In this study, in accordance with the prespecified statistical analysis plans, the efficacy, safety, and demographic analyses combined participants who received 8 weeks of therapy with the regimen of grazoprevir plus ruzasvir plus uprifosbuvir 450 mg as single entities in part A[13] with those who received grazoprevir plus ruzasvir plus uprifosbuvir 450 mg as fixed-dose combination tablets in part B. Combining the corresponding groups from part A with part B was considered appropriate to enable a more statistically robust analysis because pharmacokinetic analyses of the single entities in part A were comparable to those of the fixed-dose combination in part B. The primary endpoint was centrally reviewed by the funder.

Given the small sample sizes, no formal efficacy hypothesis testing or statistical testing between various subgroups for efficacy, presence of RASs, or baseline characteristics were done. No inferential or statistical comparisons were planned or done.

The full analysis set (FAS) included all participants who were randomly assigned and received at least one dose of study drug. Although the protocol specified that the

primary efficacy analysis would be done in the per-protocol population, the FAS analysis is presented here for a more conservative analysis of the results. Participants who were lost to follow-up, withdrew, or stopped the study for any reason, relapsed, or were re-infected were counted as failures in the FAS analysis. By contrast, the per-protocol population excluded participants who did not meet specific inclusion or exclusion criteria, those who were lost to follow-up, withdrew consent, or withdrew due to reasons unrelated to virological failure or study drug-related adverse events. Specifically, any participant who achieved SVR but was then re-infected with a different HCV strain (as determined by phylogenetic analysis) was counted as a success in the per-protocol population but as a failure in the FAS.

The resistance analysis population excluded those who discontinued for non-virological failure, were lost to follow-up, or those who had no baseline sequencing data. The safety analysis population was equivalent to the FAS, and included all participants who were randomly assigned and received at least one dose of study drug. The trials were registered at ClinicalTrials.gov, numbers NCT02332707 and NCT02332720.

Role of the funding source

Merck & Co, Inc (Kenilworth, NJ, USA) is developing the combined regimen grazoprevir, ruzasvir, and uprifosbuvir for treatment of HCV infection. The company contributed to the trial design, study execution and management, data collection, statistical analyses, and drafting of this report. The funder reviewed a final version of the paper. All coauthors had access to the study data, approved the final report, and assume full responsibility for the veracity of the data and analyses. The lead and corresponding author (EL) had full access to all data and had final responsibility for the decision to submit the manuscript for publication.

Results

Between Feb 18, 2015, and Aug 18, 2016, 664 participants infected with genotype 1, 2, or 3 and 11 participants with genotype 4 or 6 were randomly assigned to the treatment duration groups, received study medication, and comprise the FAS (figure 1). Participants infected with genotype 1, 2, or 3 (n=664) were mostly male (59%), with a median age of 54 years, mostly white race (90%), with a median baseline HCV RNA concentration of 6·3 $\log_{10}$ IU/mL and a mean body-mass index (BMI) of 27 kg/m² (table 1). All participants infected with genotypes 1 and 2 were treatment-naive, whereas 44% of those with genotype 3 infection had received previous treatment with pegylated interferon and ribavirin. Overall, 38% had cirrhosis as defined by either biopsy (n=33; 13%), Fibroscan (n=206; 83%), or Fibrosure (FibroTest) plus APRI (n=10; 4%). Participants were predominantly from North America (45%) and the European Union (39%), with about 8% each from Asia Pacific and the Middle East (table 1).

	Genotype 1 (n=176)	Genotype 2 (n=151)	Genotype 3 (n=337)
Sex			
Male	107 (61%)	86 (57%)	199 (59%)
Female	69 (39%)	65 (43%)	138 (41%)
Age (years)	55 (43–61)	57 (50–63)	52 (45–58)
Race or ethnicity*			
White	156 (89%)	135 (89%)	304 (90%)
Black (or African American)	18 (10%)	8 (5%)	4 (1%)
Hispanic or Latino	34 (19%)	38 (25%)	13 (4%)
Cirrhosis (Metavir F4)	75 (43%)	57 (38%)	117 (35%)
Body-mass index† (kg/m²)	27 (5·2)	27 (5·8)	26 (5·3)
Body-mass index ≥30 kg/m²	43 (24%)	36 (24%)	77 (23%)
Median baseline HCV RNA ($\log_{10}$ IU/mL)	6·2 (5·8–6·5)	6·4 (5·9–6·8)	6·3 (5·7–6·8)
HCV genotype (subtype)			
Genotype 1a	90 (51%)	..	..
Genotype 1b	86 (49%)	..	..
Treatment-naive	176 (100%)	151 (100%)	189 (56%)
Previous treatment with pegylated interferon and ribavirin	..	..	148 (44%)
HCV–HIV co-infected	10 (6%)	5 (3%)	12 (4%)
Geographic region			
North America	87 (49%)	87 (58%)	125 (37%)
European Union	78 (44%)	56 (37%)	128 (38%)
Asia Pacific	4 (2%)	4 (3%)	45 (13%)
Middle East	7 (4%)	4 (3%)	39 (12%)

Data are n (%), mean (SD), or median (IQR). HCV=hepatitis C virus. *Some participants identified themselves in more than one race or ethnicity category. †Body-mass index results based on 173 genotype 1, 150 genotype 2, and 337 genotype 3 participants.

Table 1: **Baseline characteristics and demographics of the full analysis set**

Among the seven participants infected with genotype 4, six were male, median age was 50 years (range 30–58), six were white, one was black, median baseline HCV RNA was 5·7 $\log_{10}$ IU/mL (IQR 5·4–6·6), and mean BMI was 25 kg/m² (SD 4·4). Among the four participants infected with genotype 6, two were male, median age was 61 years (range 43–63), median baseline HCV RNA was 6·5 $\log_{10}$ IU/mL (IQR 5·6–7·1), and mean BMI was 25 kg/m² (SD 1·6). In this cohort of 11 participants, five came from Asia Pacific and six from the Middle East.

Of the 88 individuals infected with genotype 1a or 1b in the FAS who received 8 weeks of therapy, 84 (95%) achieved SVR12 (table 2): 39 (93%) of 42 with genotype 1a

	Genotype 1			Genotype 2	Genotype 3				
	1a	1b	Total		No cirrhosis, treatment-naive	Cirrhosis, treatment-naive	No cirrhosis, treatment-experienced	Cirrhosis, treatment-experienced	Total
8 weeks without ribavirin	39/42* (93% [81–99])	45/46 (98% [88–100])	84/88 (95% [89–99])	29/32 (91% [75–98])	35/38 (92% [79–98])	..	15/15 (100% [78–100])	..	50/53 (94% [84–99])
8 weeks with ribavirin	..	..	..	25/31† (81% [63–93])	35/36 (97% [85–100])	..	13/14‡ (93% [66–100])	..	48/50 (96% [86–100])
8 weeks with or without ribavirin	39/42* (93% [81–99])	45/46 (98% [88–100])	84/88 (95% [89–99])	54/63† (86% [75–93])	70/74 (95% [87–99])	..	28/29‡ (97% [82–100])	..	98/103 (95% [89–98])
12 weeks without ribavirin	47/48§ (98% [89–100])	40/40 (100% [91–100])	87/88 (99% [94–100])	45/46¶ (98% [88–100])	35/37‖ (95% [82–99])	12/13 (92% [64–100])	14/14 (100% [77–100])	15/15 (100% [78–100])	76/79 (96% [89–99])
12 weeks with ribavirin	..	..	..	16/16 (100% [79–100])	35/35 (100% [90–100])	16/16 (100% [79–100])	14/15 (93% [68–100])	14/14 (100% [77–100])	79/80 (99% [93–100])
12 weeks with or without ribavirin	47/48§ (98% [89–100])	40/40 (100% [91–100])	87/88 (99% [94–100])	61/62¶ (98% [91–100])	70/72‖ (97% [90–100])	28/29 (97% [82–100])	28/29 (97% [82–100])	29/29 (100% [88–100])	155/159 (97% [94–99])
16 weeks without ribavirin	..	..	..	26/26 (100% [87–100])	..	13/14** (93% [66–100])	15/16 (94% [70–100])	20/20 (100% [83–100])	48/50 (96% [86–100])
16 weeks with ribavirin	..	..	..	..	..	..	..	24/25 (96% [80–100])	24/25 (96% [80–100])
16 weeks with or without ribavirin	..	..	..	26/26 (100% [87–100])	..	13/14** (93% [66–100])	15/16 (94% [70–100])	44/45 (98% [88–100])	72/75 (96% [89–99])

Data are n/N (% [95% CI]). The Clopper-Pearson exact method was used to determine two-sided 95% CIs. SVR12=sustained virological response at follow-up week 12 (proportion of participants with hepatitis C virus RNA concentrations of less than the lower limit of quantitation [<15 IU/mL] at 12 weeks after the end of treatment). *One participant achieved SVR8 but was re-infected with a different hepatitis C virus strain as determined by phylogenetic analysis at follow-up week 12. †One participant discontinued at day 5 due to drug-related adverse events of fatigue and malaise; one participant withdrew consent. ‡One participant was lost to follow-up. §One participant died due to study-drug-unrelated bacterial sepsis. ¶One participant was lost to follow-up after achieving SVR8. ‖One participant withdrew from treatment due to pregnancy and then was lost to follow-up. **One participant was lost to follow-up.

Table 2: **SVR12 of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin by duration of treatment, presence or absence of cirrhosis, and previous treatment history (full analysis set)**

and 45 (98%) of 46 with genotype 1b (figure 2, table 2). After 8 weeks of treatment, three participants experienced virological relapse (two with genotype 1a and one with genotype 1b), and one individual with genotype 1a achieved SVR8 but was re-infected with a different HCV type (as determined by phylogenetic analysis done at follow-up week 12; figure 2). 87 (99%) of 88 participants infected with genotypes 1a and 1b who received 12 weeks of therapy achieved SVR12 (table 2): 47 (98%) of 48 with genotype 1a infection and 40 (100%) of 40 with genotype 1b infection. There were no virological relapses in this group, but one individual with cirrhosis with genotype 1a infection who was assigned 12 weeks of treatment died due to bacterial sepsis that was deemed unrelated to study drug. Cirrhosis status did not impact SVR12 among participants infected with genotype 1 (table 2). SVR12 was achieved in 54 (86%) of the 63 participants without cirrhosis who were infected with genotype 2 who received 8 weeks of therapy with and without ribavirin (figure 2, table 2); seven participants experienced virological relapse, one participant in a ribavirin-containing group discontinued at day 5 due to drug-related adverse events of fatigue and malaise, and one was lost to follow-up (table 2). SVR12 was achieved in 61 (98%) of 62 participants who received 12 weeks of therapy with and without ribavirin (table 2); one participant was lost to follow-up in the 12 weeks without ribavirin group, and none experienced virological relapse. In particular, SVR12 was achieved in 45 (98%) of the 46 participants infected with genotype 2 who received 12 weeks of therapy without ribavirin; one participant was lost to follow-up (this person achieved SVR8 but did not return for the follow-up week 12 visit) and none experienced virological relapse. SVR12 was achieved in all (100%) of the 26 participants with genotype 2 infection who received 16 weeks of therapy. Neither cirrhosis status nor the addition of ribavirin affected SVR among those with genotype 2 infection who received 12 or 16 weeks of treatment (table 2).

SVR12 was achieved in 98 (95%) of the 103 participants without cirrhosis who were infected with genotype 3 who received 8 weeks of therapy with and without ribavirin (figure 2, table 2); four participants experienced virological relapse and one was lost to follow-up (figure 2). SVR12 was achieved in 155 (97%) of 159 participants with and without cirrhosis who received 12 weeks of therapy with and without ribavirin (figure 2, table 2); three participants experienced virological relapse and one withdrew from treatment due to pregnancy and was subsequently lost to follow-up. In the 12-week treatment group, the addition of ribavirin, cirrhosis status, and previous treatment with pegylated interferon and ribavirin did not substantially affect SVR12 (table 3). In treatment-experienced participants with cirrhosis who were infected with genotype 3 and treated for 12 weeks without ribavirin, SVR12 was achieved in all 15 participants (100%; table 2). SVR12 was achieved in 72 (96%) of 75 participants who received 16 weeks of therapy with and without ribavirin (figure 2,

table 2); two participants experienced virological relapse and one was lost to follow-up (table 3).

To better understand the differences in treatment responses between regimens and subpopulations, efficacy was also analysed in the per-protocol population (appendix p 15). In the per-protocol population, seven participants were excluded. Additionally, the one individual infected with genotype 1a who achieved SVR8 but was re-infected with a different HCV strain was counted as a success in the per-protocol analysis. Thus, the efficacy results for the per-protocol analysis are slightly higher than those for the FAS, which included participants who were lost to follow-up or discontinued due to administrative reasons.

The preliminary results from the participants infected with genotypes 4 and 6 show that 100% achieved SVR12, including the seven treatment-naive participants without cirrhosis who were infected with genotype 4 who received 8 weeks of combined therapy (SVR12 100% [95% CI 59–100]), and the four treatment-naive participants without cirrhosis who were infected with genotype 6 who received 12 weeks of therapy (SVR12 100% [40–100]).

There were no documented virological failures after follow-up week 12. Between follow-up week 12 and 24, however, ten participants who achieved SVR12 were lost to follow-up (four with genotype 1a treated for 12 weeks [SVR24: 43 (90%) of 48], one with genotype 1b treated for 8 weeks [SVR24: 44 (96%) of 46], one with genotype 2 treated for 12 weeks [SVR24: 60 (97%) of 62], two with genotype 3 treated for 8 weeks [SVR24: 96 (93%) of 103], and two with genotype 3 treated for 12 weeks [SVR24: 153 (96%) of 159]; appendix p 5).

Treatment with grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin was generally well tolerated (table 3). Two (<1%) of 664 participants had serious adverse events that were drug-related and both were considered related to ribavirin only. There was one death; one person infected with genotype 1 died due to a study drug-unrelated bacterial sepsis. There were nine study medication discontinuations due to drug-related adverse events, and in four of these cases only ribavirin was discontinued. A higher proportion of adverse events and drug-related adverse events were reported among those in the ribavirin-containing groups. The four adverse events leading to discontinuation that were considered related to the drug combination included: fatigue and malaise; nausea and feeling cold; and two cases of transaminitis (elevation of both ALT and AST), one of which was confounded by gallstones. The most frequent study drug-related adverse events in more than 10% of participants were headache (22%), fatigue (19%), and nausea (13%; table 3).

Grazoprevir-related late elevations of aminotransferases occurred among six (1%) of 664 participants, without clinically meaningful elevations in bilirubin concentrations or compromise in liver function; this rate is similar to rates previously reported among those being treated with elbasvir plus grazoprevir.[14] Treatment with grazoprevir, ruzasvir, and uprifosbuvir was not associated with cardiac or renal signals and tolerability was similar in participants with and without cirrhosis,

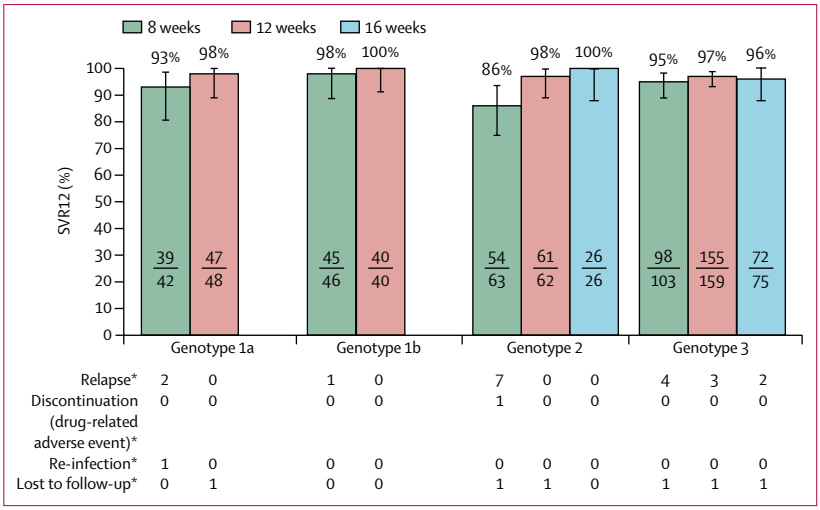

Figure 2: **SVR12 for grazoprevir, ruzasvir, and uprifosbuvir with and without ribavirin by HCV genotype and duration of treatment (full analysis set)**

The full analysis set population included all participants who received at least one dose of study drug. The two-sided 95% CI was calculated for the SVR12 for each group separately using the Clopper-Pearson method. SVR12=sustained virological response at follow-up week 12 (proportion of participants with HCV RNA concentrations less than the lower limit of quantitation [<15 IU/mL] at 12 weeks after the end of treatment). HCV=hepatitis C virus. *At follow-up week 12, 19 participants experienced virological relapse and eight participants discontinued, were reinfected or lost to follow-up: genotype 1a, 8 weeks, no ribavirin: one participant achieved SVR8 but was re-infected with a different HCV strain as determined by phylogenetic analysis done at follow-up week 12; genotype 1a, 12 weeks, no ribavirin: one participant died due to study drug-unrelated bacterial sepsis; genotype 2, 8 weeks, with ribavirin: one participant discontinued at day 5 due to drug-related adverse events of fatigue and malaise; one participant was lost to follow-up; genotype 2, 12 weeks, no ribavirin: one participant was lost to follow-up; genotype 3, 8 weeks, with ribavirin: one participant was lost to follow-up; genotype 3, 12 weeks, no ribavirin: one participant withdrew due to pregnancy, then was lost to follow-up; genotype 3, 16 weeks, no ribavirin: one participant was lost to follow-up.

	Grazoprevir, ruzasvir, and uprifosbuvir without ribavirin (n=462)	Grazoprevir, ruzasvir, and uprifosbuvir with ribavirin (n=202)	Overall (n=664)
One or more adverse events	321 (69%)	173 (86%)	494 (74%)
Drug-related adverse events	165 (36%)	135 (67%)	300 (45%)
Serious adverse events	11 (2%)	5 (2%)	16 (2%)
Drug-related serious adverse events	0	2 (1%)*	2 (<1%)
Deaths	1 (<1%)†	0	1 (<1%)
Discontinuation due to adverse event	3 (1%)	6 (3%)‡	9 (1%)‡
Drug-related late ALT or AST >5 × ULN	6 (1%)	0	6 (1%)
Creatinine grade 1 (1·1–1·3 × ULN)	3 (1%)	0	3 (<1%)
Creatinine grade 2 (1·4–1·8 × ULN)	1 (<1%)	1 (<1%)	2 (<1%)
Most common adverse events (>10%)			
Headache	88 (19%)	55 (27%)	143 (22%)
Fatigue	70 (15%)	59 (29%)	129 (19%)
Nausea	52 (11%)	31 (15%)	83 (13%)

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. ULN=upper limit of normal. *One participant infected with genotype 3 had an exacerbation of chronic obstructive pulmonary disease related to ribavirin; one participant infected with genotype 2 had a worsening of depression related to ribavirin. †One participant infected with genotype 1 died due to a study drug-unrelated bacterial sepsis. ‡Four participants discontinued ribavirin only.

Table 3: **Safety and tolerability (full analysis set)**

as well as in HCV mono-infected and HCV–HIV co-infected individuals.

Among the seven participants infected with genotype 4 and four participants infected with genotype 6, preliminary data indicate that six had one or more adverse events. Three individuals had drug-related adverse events, as determined by the respective investigators. There were no serious adverse events and no discontinuations among participants infected with genotypes 4 and 6 (data not shown).

Across all treatment groups for genotypes 1–3, more than 60% of participants had HCV RNA less than the lower limit of quantitation (<15 IU/mL) by treatment week 3, 80% or more had HCV RNA less than the lower limit of quantitation by treatment week 4, and all but nine (1%) of 664 participants had HCV RNA less than the lower limit of quantitation by treatment week 6 (appendix pp 12–14). Of these nine participants, one participant infected with genotype 2 discontinued treatment after 5 days of treatment due to study drug-related adverse events and one participant infected with genotype 1 died of bacterial sepsis following treatment week 6. The remaining seven participants (one with genotype 1a, two with genotype 2, and four with genotype 3) all achieved SVR12.

All 19 virological failures experienced virological relapse after the end of treatment; there were no breakthroughs. Among the two participants infected with genotype 1a who experienced virological relapse, one had HCV RNA less than the lower limit of quantitation by treatment week 3 and one by treatment week 6; the one participant infected with genotype 1b who experienced virological relapse had HCV RNA less than the lower limit of quantitation by treatment week 3. Among the seven participants infected with genotype 2 who experienced virological failure, four had HCV RNA less than the lower limit of quantitation by treatment week 2, and one each by treatment weeks 3, 4, and 6; five of them had the NS5A L31M RAS present at baseline. Among the nine participants infected with genotype 3 who experienced virological failure, one had HCV RNA less than the lower limit of quantitation by treatment day 7, five by treatment week 2, and one each by treatment weeks 3, 6, and 12; five of them had the NS5A Y93H RAS present at baseline.

175 participants infected with genotype 1 had available baseline NGS data. Among those infected with genotype 1a the prevalence of RASs in NS3, NS5A, and NS5B was 44 (49%) of 89, nine (10%) of 89, and one (1%) of 88, respectively (appendix p 17). Among participants infected with genotype 1b, the prevalence of RASs in NS3, NS5A, and NS5B was 68 (79%) of 86, 23 (27%) of 86, and 31 (36%) of 86, respectively. There was no substantial impact of baseline RASs in NS3, NS5A, or NS5B on the SVR12s among participants infected with genotype 1 treated for either 8 or 12 weeks. After 12 weeks of treatment, SVR12 was achieved in 87 (100%) of 87 participants infected with genotype 1 regardless of subtype or presence of baseline NS5A RASs. Neither of the two participants infected with genotype 1a who relapsed following 8 weeks of therapy had any baseline RASs; the one participant infected with genotype 1b who relapsed following 8 weeks of therapy had baseline RASs in NS3 (Y56F, V170I) and NS5B (C316N), but not in NS5A (appendix p 17).

Among the 144 participants infected with genotype 2 with available baseline NGS data, the prevalence of RASs in NS3, NS5A, and NS5B was 142 (100%) of 142, 142 (99%) of 144, and three (2%) of 144, respectively (appendix p 17). Baseline RASs at NS5A aminoacid 31 were detected in 70 (49%) of 144 with genotype 2 infection, and were similar among the different treatment groups (range 44–54%; appendix p 6; and data not shown). In the 8-week treatment groups, the SVR12 for those with genotype 2 infection with and without baseline L31M substitutions was 81% and 94%, respectively (appendix p 6). Among the 59 participants in the 8-week treatment groups, those infected with genotype 2a had a lower SVR12 (69%) compared with those infected with genotype 2b (97%), and the L31M substitution was observed more frequently among those with genotype 2a compared with genotype 2b (92% *vs* 31%). Of the seven participants with genotype 2 infection who failed after 8 weeks of treatment, five had L31M at baseline, and four were infected with genotype 2a and one with genotype 2b. All of the participants receiving 12 or 16 weeks of treatment achieved SVR12 regardless of presence of L31M at baseline (appendix pp 6, 17).

Among the 334 participants infected with genotype 3 with available baseline NGS data in at least one gene region, the prevalence of RASs in NS3, NS5A, and NS5B was 309 (95%) of 324, 175 (52%) of 334, and seven (2%) of 328, respectively (appendix p 17). Overall, baseline RASs in NS3 or NS5A did not substantially affect SVR12, which ranged from 94% to 100% across treatment groups (appendix p 17). The NS5A RAS Y93H was detected at baseline among four (4%) of 102 and seven (4%) of 158 participants in the 8-week and 12-week groups, respectively; of these two (50%) and five (71%) achieved SVR12 in the 8-week and 12-week groups, respectively (appendix p 6). Of the three participants infected with genotype 3 who had virological relapse after 12 weeks of treatment, only one developed treatment-emergent RASs, NS5A Y93H and NS3 Q168L. This person was the only one of the 664 participants (<1%) in this study to develop treatment-emergent RASs.

Discussion

Results of these phase 2 clinical trials show that the combination of grazoprevir, ruzasvir, and uprifosbuvir given for 12 weeks without ribavirin is well tolerated and highly effective in treating individuals infected with HCV genotypes 1, 2, and 3. Addition of ribavirin to this combination did not improve SVR12 for any treatment

duration, and an 8-week treatment regimen was highly efficacious (SVR12 94–95%) in those infected with HCV genotypes 1 (non-cirrhotic and cirrhotic) and 3 (non-cirrhotic). In participants infected with genotype 2, 12 weeks of treatment was more effective than 8 weeks (SVR12, 98% *vs* 86%). The lower SVR12 following 8 weeks of treatment was not predicted based on the in-vitro activities of these drugs against a genotype 2 (JFH-1) replicon (appendix p 16). These clinical efficacy results together with in-vitro data suggest that treatment duration might affect the efficacy of this regimen among people infected with genotype 2, particularly in those with certain baseline characteristics, such as the NS5A L31M substitution.

Baseline RASs did not affect the efficacy of grazoprevir, ruzasvir, and uprifosbuvir in individuals infected with genotype 1. The overall impact of baseline RASs on efficacy in participants infected with genotype 2 could not be accurately assessed due to the small number of participants without NS3 and NS5A RASs and of those with NS5B RASs. The high prevalence of NS3 and NS5A RASs in this group reflects the inclusion of all polymorphisms that have been reported to be associated with resistance to either drug class. Although the in-vitro potency of ruzasvir in a genotype 2a replicon carrying a L31M substitution is reduced by about 60 times, the impact of baseline L31M RAS in individuals infected with genotype 2 could be overcome by extending treatment from 8 weeks (SVR12 88%) to 12 weeks (SVR12 100%; appendix p 17). The lower SVR12 observed with the 8-week regimen appeared to correlate with the presence of baseline L31M substitution, regardless of genotype 2 subtype. Baseline Y93H RASs in those infected with genotype 3 might impact SVR12, which is consistent with in-vitro susceptibility data showing that the efficacy of ruzasvir is reduced by about 750 times in a genotype 3 replicon containing a Y93H substitution. The SVR12 among participants infected with genotype 3 with a baseline Y93H RAS who were treated with the currently approved and recommended regimen of 12 weeks of sofosbuvir plus velpatasvir was reported to be 84%.[6,15,16] The SVR12 for grazoprevir, ruzasvir, and uprifosbuvir in this subpopulation needs to be further investigated in larger trials, since there were very small numbers of people infected with genotype 3 with Y93H RASs enrolled in C-CREST-1 and C-CREST-2. Notably, of the 19 participants who experienced virological relapse in these studies, only one developed treatment-emergent RASs, demonstrating the overall high barrier to the development of resistance with this three-drug DAA regimen.

This three-drug combination for 12 weeks appears to be highly efficacious in individuals with compensated cirrhosis; an 8-week duration was not evaluated in those with genotype 2 or 3 infection and cirrhosis. The efficacy after 12 weeks among participants with cirrhosis infected with genotype 3 who had previously received treatment with pegylated interferon and ribavirin was 15 of 15 (100%), suggesting that this regimen might prove to be a better treatment option for this subpopulation than other currently available regimens. For example, the efficacy rate after 12 weeks of treatment with sofosbuvir plus velpatasvir among this group was reported to be 89%.[15]

The limitations of this study include the small sample sizes of subgroups, which prevented meaningful statistical comparisons between different treatment regimens. The relatively small sizes also limited the ability to draw conclusions about the relationship between baseline characteristics, including RASs, with SVR12s. Furthermore, although early viral kinetics alone did not appear to be a strong predictor of individual efficacy for this highly efficacious triple DAA regimen, the small sample sizes did not allow for robust efficacy projections. Additionally, this study did not include an 8-week treatment duration for those with genotype 2 or 3 and cirrhosis. Lastly, although the preliminary efficacy data in participants infected with genotypes 4 and 6 appear promising, the number of such participants was very small and there were no participants infected with genotype 5 enrolled. Nonetheless, because ruzasvir, grazoprevir, and uprifosbuvir all exhibit a pan-genotypic spectrum of activity in replicon-based assays, it is anticipated that this three-drug regimen should be effective against genotypes 4, 5, and 6. Further clinical studies in those infected with these genotypes will help assess the ability of this regimen to achieve clinical cure in these populations.

Most currently approved treatments for HCV do not have pan-genotypic efficacy, with the exception of 12 weeks of sofosbuvir plus velpatasvir. Glecaprevir plus pibrentasvir is currently being investigated as a pan-genotypic regimen in individuals infected with HCV with and without cirrhosis.[17–20] Results from the current studies support further investigation of grazoprevir, ruzasvir, and uprifosbuvir as a pan-genotypic regimen in individuals infected with HCV with and without cirrhosis, and suggest that this combination has the potential to provide a safe, single duration regimen in most populations, including individuals with cirrhosis infected with genotype 3 who had previously received treatment with pegylated interferon and ribavirin. These results need to be confirmed in larger phase 3 trials and further investigated among those infected with genotypes 4–6.

Contributors

EL was the principal investigator of the trial, was involved in data collection, data analysis, data interpretation, and contributed to the writing of the Article. MB and EMY were involved in data collection, data interpretation, and critically reviewed the Article. JMV was involved in data collection, study design, data interpretation, and critically reviewed the Article. PLA, TIH, and SB were involved in data collection, data interpretation, and critically reviewed the Article. PJR was involved in data interpretation and writing the Article. BP and LJ were involved in data collection, data analysis, data interpretation, and critically reviewed the Article. WG was involved in study design, data collection, data interpretation, and critically reviewed the Article. H-CH was involved in data analysis, data interpretation, contributed to the writing of the

Article, and produced some of the figures in the Article. AS was involved in data collection, data analysis, and critically reviewed the Article. BT and DF were involved in study design, data interpretation, and critically reviewed the Article. JJL was involved in study design, data analysis, contributed to the writing, production of figures, and critically reviewed the Article. BM, AG, F-HS, and WWY were involved in data collection, data analysis, data interpretation, and contributed to the writing of the Article. HL was involved in data analysis, data interpretation, and critically reviewed the Article. SW was involved in study design, data analysis, data interpretation, and critically reviewed the Article. FJD was involved in data interpretation, contributed to the writing and the production of figures for the Article, and did the literature search. RMP was involved in data analysis, data interpretation, contributed to the writing of the Article, and critically reviewed the Article. B-YTN was involved in data collection, study design, data analysis, data interpretation, and contributed to the writing of the Article. JW was involved in study design and critically reviewed the Article. MNR was involved in study design, data interpretation, and critically reviewed the Article. EB was involved in study design, data analysis, data interpretation, contributed to the writing of the Article, and critically reviewed the Article. JRB was involved in study design, data interpretation, and contributed to the writing of the Article.

Declaration of interests

EL has received grants (paid to him) and consulting fees or honoraria (paid to his institution) from Merck & Co, Inc; he reports consultancies for AbbVie, Achillion Pharmaceuticals, BioCryst, Biotica, Bristol-Myers Squibb, Enanta, Gilead Sciences, Indenix Pharmaceuticals, Janssen, Merck & Co, Inc, Novartis, Santaris Pharmaceuticals, Regulus, Theravance, and Vertex Pharmaceuticals; he also reports grants or grants pending from AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Idenix Pharmaceuticals, Janssen, Merck & Co, Inc, Novartis, Presidio, Roche, Salix, Santaris Pharmaceuticals, Theravance, and Vertex Pharmaceuticals; and payment for lectures or service on speaker's bureaus for AbbVie, Gilead, and Janssen. MB reports personal fees from Gilead, MSD, and AbbVie, during the conduct of the study. JMV reports grants from Merck & Co, Inc, during the conduct of the study; grants from AbbVie, Bristol-Meyers Squibb, Conatus, Genentech, Gilead, Merck & Co, Inc, Novartis, and Sundise, and compensation for being a scientific adviser to AbbVie, Bristol-Meyers-Squibb, Genentech, Gilead, Merck & Co, Inc, Novartis, and Sundise, outside the submitted work. SB reports personal fees from MSD, Gilead, and AbbVie, outside the submitted work. PJR reports personal fees from Merck & Co, Inc, Gilead Sciences, and AbbVie, outside the submitted work. TIH reports grants and personal fees from MSD, outside the submitted work. BM reports personal fees from MSD, Janssen Therapeutics, AbbVie, Boehringer Ingelheim, and BMS, and grants and personal fees from Gilead during the conduct of the study. BP reports grants and personal fees from Merck & Co, Inc, during the conduct of the study; grants and personal fees from Gilead and AbbVie, outside the submitted work. WG, H-CH, AS, BT, DF, JJL, AG, HL, F-HS, SW, FJD, WWY, RMP, B-YTN, MNR, EB, and JRB are employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA, and might own stock or hold stock options in the Company. JW is a former employee of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA, and might own stock or hold stock options in the Company. EMY reports grants from Merck & Co, Inc, during the conduct of the study; grants from AbbVie, Gilead Sciences, Janssen, Springbank, Intercept, and Genfit, and personal fees from Merck Canada, Gilead Canada, AbbVie Canada, and Celgene Canada, outside the submitted work. PLA and LJ declare no competing interests.

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