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Real-world safety and effectiveness of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in hepatitis C virus genotype 1- and 4-infected patients with diverse comorbidities and comedications: A pooled analysis of post-marketing observational studies from 13 countries

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Summary

Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin (OBV/PTV/r ± DSV ± RBV) regimens show high efficacy and good tolerability in clinical trials for chronic hepatitis C virus (HCV) genotypes (GT) 1 or 4. To evaluate whether these results translate to clinical practice, data were pooled from observational studies across 13 countries. Treatment-naïve or -experienced patients, with or without cirrhosis, received OBV/PTV/r ± DSV ± RBV according to approved local labels and clinical practice. Sustained

Abbreviations: ACE, angiotensin-converting-enzyme; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; CI, confidence intervals; CPSFU, core population with sufficient follow-up; CrCl, creatinine clearance; CTCAE, Common Terminology Criteria for Adverse Events; DAA, direct-acting antiviral; DSV, dasabuvir; EOT, end of treatment; GERD, gastro-esophageal reflux disease; GT, genotype; HCV, hepatitis C virus; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; r, ritonavir; SVR12, sustained virologic response at post-treatment Week 12.

Peter Ferenci and Stefan Bourgeois should be considered joint first author.

Clinical Trial Registration: Each of the trials included in this post-marketing observational study were registered at ClinicalTrials.gov. Their identification numbers are as follows: NCT02582658, NCT02581163, NCT02581189, NCT02851069, NCT02618928, NCT02615145, NCT02725866, NCT02636608, NCT02582671, NCT02803138, NCT02798315, NCT02640547 and NCT02807402.

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virologic response at post-treatment Week 12 (SVR12), adverse events (AEs) and co-medication management were assessed for patients initiating treatment before 1 June 2017. The safety population included 3850 patients who received ≥ 1 dose of study drug. The core population (N = 3808) further excluded patients with unknown GT or cirrhosis status, or who received off-label treatment. Patients had HCV GT1a (n = 732; 19%), GT1b (n = 2619; 69%) or GT4 (n = 457; 12%). In 3546 patients with sufficient follow-up data at post-treatment Week 12, the SVR12 rate was 96% (n/N = 3401/3546 [95% CI 95.2-96.5]). In patients with or without cirrhosis, SVR12 was comparable (96%). In patients with HCV GT1a, GT1b or GT4, SVR12 rates were 93%, 97% and 94%. In GT1b-infected patients with planned treatment for 8 weeks, SVR12 was 96%. In patients with ≥ 1 comorbidity (67%), SVR12 was 95%. 58% of patients received ≥ 1 comedication, and there was minimal impact on SVR12 rates using comedications for peptic ulcers and gastro-esophageal reflux disease, statins, antipsychotics or antiepileptics. Most comedications were maintained during treatment although 58% of patients changed their statin medication. AEs and serious AEs occurred in 26% and 3% of patients. Post-baseline Grade 3-4 laboratory abnormalities were rare (<3%), and discontinuation rates were low (<4%). Real-world evidence confirms the effectiveness of OBV/PTV/r \pm DSV \pm RBV in patients with HCV GT1 or GT4, regardless of common comorbidities or comedications, and is consistent with clinical trial results. Adverse safety outcomes may be limited by underreporting in the real-world setting.

KEYWORDS

comorbidity, direct-acting antiviral, drug-drug interaction, hepatitis C virus, real-world evidence

1 | INTRODUCTION

Since their introduction in 2013, second-generation direct-acting antiviral (DAA) drugs have improved the efficacy, safety and tolerability of treatment for chronic hepatitis C virus (HCV) infection. All-oral, interferon-free DAA combination regimens comprising ombitasvir/paritaprevir/ritonavir + dasabuvir (OBV/PTV/r+DSV) \pm ribavirin (RBV) and OBV/PTV/r + RBV were approved for use in the United States and Europe in 2014-2015¹⁻⁴ and are recommended for the treatment of HCV genotypes (GT) 1 and 4, respectively.^{5,6} In GT1a-infected patients without cirrhosis, OBV/PTV/r + DSV + RBV is administered for 12 weeks, or for 24 weeks in patients with compensated cirrhosis. In GT1b-infected patients without cirrhosis or with compensated cirrhosis, OBV/PTV/r + DSV is administered for 12 weeks (or 8 weeks with mild fibrosis [F0-F2]).^{2,3} In GT4-infected patients, OBV/PTV/r + RBV is administered for 12 weeks regardless of cirrhosis status.¹⁻⁴ These multitargeted DAA regimens have shown good tolerability and high rates of sustained virologic response at post-treatment Week 12 (SVR12) in a broad range of adult patients in pivotal clinical trials.⁷⁻¹² As of April 2017, OBV/PTV/r + DSV regimens are approved in more than 80 countries, and OBV/PTV/r in more than 50 countries.

Notwithstanding the success of DAA regimens, barriers to HCV treatment initiation remain, with the presence of comorbidities and the potential risk for drug-drug interactions (DDIs) cited as common impediments.⁵ Patients with chronic HCV infection have a high burden of comorbid medical and psychiatric conditions,¹³⁻¹⁵ which are often managed with multiple comedications.¹⁶ Among patients treated with currently available DAA drugs who are taking comedications, at least 30% are potentially at risk for clinically significant DDIs,¹⁷ although these risks vary between individual drugs. Clinically significant DDIs with commonly prescribed drugs and over-the-counter medications have been established for OBV/PTV/r \pm DSV based on drug interaction studies.

In clinical practice, the effectiveness of DAA therapies may be lower than in clinical trials because patient populations tend to be more diverse (eg patients may be older, have more advanced disease or have additional comorbidities) and less adherent to treatment regimens.¹⁸ Furthermore, clinical trials are designed to establish efficacy outcomes of investigative drugs and are conducted in controlled settings, with strict eligibility criteria that are intended to enroll well-defined trial populations with limited comorbidities or comedications to mitigate any unwarranted influence on treatment safety and efficacy outcomes. Therefore, the results from clinical

trials may not be comparable to those from daily clinical practice. Studies using real-world data collected during routine clinical care provide additional evidence of treatment safety and effectiveness, which complements the results from clinical trials. Understanding the safety and effectiveness of DAA regimens in real-world settings is important to help guide patients and healthcare providers in clinical decision-making as well as to help inform regulatory decision-making.¹⁹ At present, data assessing the real-world effectiveness of OBV/PTV/r ± DSV ± RBV regimens in patients with HCV are limited.

In this pooled analysis of post-marketing observational studies, we evaluated the real-world safety and effectiveness of OBV/PTV/r ± DSV ± RBV regimens, as well as comedication management, in clinical practice in patients chronically infected with HCV GT1 or GT4.

2 | MATERIALS AND METHODS

2.1 | Study design

This was an analysis of data pooled from AbbVie-sponsored, prospective, observational studies conducted at 289 sites in 13 countries: Austria (NCT02582658), Belgium (NCT02581163), Canada (NCT02581189), Colombia (NCT02851069), France (NCT02618928), Germany (NCT02615145), Greece (NCT02725866), Hungary (NCT02636608), Ireland (NCT02582671), Israel (NCT02803138), Kuwait (NCT02798315), Poland (NCT02640547) and Romania (NCT02807402). In some countries, the studies are still ongoing. All eligible patients were followed from treatment initiation until 12 weeks after the end of treatment (EOT) (or until premature discontinuation, or in accordance with local clinical practice).

Data were recorded in English by each participating centre via a centralized electronic data capture system using web-based case report forms (eCRF). Examinations, diagnostic measures, laboratory assessments, findings and observations routinely performed in patients with chronic HCV infection included in this cohort were transcribed by the investigator or designee from the source documents into the eCRF.

Each study was conducted in accordance with local laws and regulations and received the required approvals from the responsible regulatory authorities, ethics committees and/or competent authorities.

2.2 | Study populations and treatments

Analyses were performed in the following populations. The safety population included all male or female patients who were ≥18 years of age, chronically infected with HCV GT1 or GT4 (or with missing GT information), and who had received ≥1 dose of study drug. Patients who were treatment-naïve or -experienced (previous treatment with interferon- or DAA-based regimens) were included, as were patients with or without cirrhosis. Patients were excluded if

they had a missing treatment start date or initiated planned treatment after 1 June 2017, or their treatment group was missing.

The core population further excluded from the safety population patients who did not have confirmed chronic HCV infection with GT1 or GT4, patients with cirrhosis and GT1a infection not receiving RBV, patients with GT1 for whom OBV/PTV/r instead of OBV/PTV/r + DSV was prescribed, patients with GT4 not receiving RBV, and patients with unknown HCV GT or cirrhosis status. Patients with missing SVR12 values were counted as nonresponders in the core population.

The core population with sufficient follow-up (CPSFU) included patients from the core population apart from those with a documented virologic response at their last on-treatment or post-treatment measurement but with no HCV RNA measurements more than 70 days post-treatment for reasons not related to safety or effectiveness, or patients with no HCV RNA measurements post-baseline or no treatment end date for reasons not related to safety or effectiveness (eg lost to follow-up, consent withdrawal).

Patients infected with HCV GT1a received OBV/PTV/r + DSV ± RBV regimens for planned treatment durations of 12 or 24 weeks. Patients infected with HCV GT1b received OBV/PTV/r + DSV ± RBV regimens for planned treatment durations of 12 or 24 weeks. In some cases, GT1-infected patients did not receive DSV. The HCV GT1-infected population also included patients with a planned treatment duration of 8 weeks because treatment-naïve patients with minimal to moderate fibrosis (F0-F2) may have been considered for this shorter treatment duration based on findings from the GARNET study and according to local label updates.^{2,20} Patients infected with HCV GT4 received OBV/PTV/r ± DSV + RBV regimens for planned treatment durations of 12 or 24 weeks. In some cases, patients infected with GT4 did not receive RBV. The recommended dosage of OBV/PTV/r was 25 mg/150 mg/100 mg once daily, and DSV was 250 mg twice daily; weight-based RBV was administered according to local label. The choice of treatment regimen was at the discretion of the healthcare provider and was consistent with the recommended label or with local clinical practice.

2.3 | Assessments

SVR12 was defined as an HCV RNA concentration <50 IU/mL at 12 weeks after EOT (70-126 days after the last dose). HCV RNA measurements were considered <50 IU/mL if HCV RNA was undetectable and the lower limit of detection of the assay was ≤50 IU/mL; or HCV RNA was unquantifiable and the lower limit of quantification was ≤50 IU/mL (ie HCV RNA detectable but below the limit of quantification).

Virologic breakthrough was defined as ≥1 documented HCV RNA measurement <50 IU/mL followed by HCV RNA ≥50 IU/mL during treatment. Virologic relapse was defined as HCV RNA <50 IU/mL at EOT followed by post-treatment HCV RNA ≥50 IU/mL in patients who completed treatment (not shortened by more than 7 days) (see Supplementary Materials for missing values imputation.)

Demographics and clinical characteristics were assessed at baseline. Patient-reported comedication use during treatment was evaluated. The administration of any oral or injected medications, which were taken at the time when the decision was made to initiate DAA treatment until after the last DAA dose, was documented (including opiate substitution, contraceptives/hormonal replacements and herbal supplements) (see Supplementary Materials for information on comedication coding).

The management profiles of commonly used comedICATIONS with potential DDIs with DAAs within the following disease-indicated drug classes were evaluated (all drugs within each class were considered): drugs for peptic ulcers and gastro-esophageal reflux disease (GERD), cholesterol-lowering drugs (statins), antipsychotic drugs and antiepilepsy drugs (see Table S1 for the list of drugs in each class). Changes in the management profiles of patients' comedICATIONS before or during DAA treatment were classified according to the following categories:

- comedication maintained without change (dose modifications or temporary interruptions were not documented);
- permanently discontinued before or during DAA treatment, or subsequently resumed post-treatment;
- comedication was permanently or temporarily replaced or a substitute drug used at the start of or during treatment;
- new comedICATIONS were introduced during treatment.

Safety was assessed at each visit using the incidence of adverse events (AEs) and abnormal laboratory measurements. All treatment-emergent AEs were collected with onset between treatment initiation and EOT (or treatment initiation plus planned treatment duration when treatment end was missing) plus 30 days post-treatment, including AEs with missing onset date and treatment-related AEs irrespective of onset. AEs were reported by the investigator and coded according to MedDRA (Medical Dictionary for Regulatory Activities, McLean, VA, USA) system organ class and preferred terms (versions 18.0, 19.0, 19.1, 20.0 and 20.1). Abnormal laboratory measurements were evaluated in patients with known treatment end date and ≥ 1 post-nadir visit for alanine aminotransferase (ALT) or aspartate transaminase (AST), and ≥ 1 post-baseline measurement for haemoglobin and creatinine clearance (CrCl). The maximum grades at any post-nadir visit (including baseline) for ALT and AST or any post-baseline visit (regardless of the baseline value) for haemoglobin and CrCl through to EOT were summarized (see Table S2A for severity grades).

2.4 | Statistical analysis

Demographics and baseline characteristics, including comorbidities, for the core population were summarized descriptively. The percentage of patients who achieved SVR12 was evaluated in the CPSFU population and stratified by genotype (or subtype), cirrhosis status, comorbidity, prior HCV treatment experience and according to RBV coadministration. SVR12 rates were also assessed in patients who completed their full course of treatment (ie not shortened by

more than 7 days). In each case, 2-sided 95% confidence intervals (CI) for the binomial proportion were calculated using Wilson's score method. All treatment-emergent AEs and laboratory abnormalities were assessed in the safety population and were summarized descriptively. Common treatment-emergent AEs were defined as those reported in $\geq 5\%$ of patients at the preferred term level. Comedication use during the DAA-treatment period and changes in comedication management were summarized descriptively for the safety population. Multiple treatments were possible per patient. Patients reporting the use of more than 1 comedication for a given drug class or treatment management profile were counted only once for that combination. All statistical analyses were conducted by Prometris GmbH (Mannheim, Germany) using the SAS[®] software package (version 9.4; SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

This pooled analysis included patient-level data from 289 sites. Of these, 98% were based in urban locations and most sites were either academic or university hospitals (39%), or private practices or hospitals (33%) (Figure S1A). Most principal investigators at each site were either hepatologists (69%) and/or gastroenterologists (53%) (Figure S1B). In terms of patient visits per month, 19% of sites saw <25 HCV-infected patients and 37% saw between 25 and 50 HCV-infected patients.

The date of the first patient visit was 6 October 2015. As of 19 February 2018, 4088 patients were enrolled in this study; 238 patients were excluded, and 3850 met the criteria for inclusion in the safety population. One GT4-infected patient from the safety population who had unconfirmed chronic HCV infection was excluded from the core and CPSFU populations. After applying further exclusion criteria, 3808 and 3546 patients remained in the core and CPSFU populations, respectively (Figure S2).

3.1 | Baseline demographics and clinical characteristics

In the core population, 2034 patients (53%) were male, 3375 (89%) were white, and the median age was 57 years (range 18-90) (Table 1). A total of 732 patients (19%) had HCV GT1a (including 11 patients with GT1a/GT1b, 16 patients with GT1 unknown subtype and two patients with GT1 unknown subtype/GT4 unknown subtype), 2619 (69%) had GT1b (including one patient with GT1b/GT4 unknown subtype), and 457 (12%) had GT4 (non-GT1). The distribution of HCV GT1 and GT4 for each country is shown in Figure S3, and only Kuwait had a greater percentage of patients infected with GT4 than GT1 (69% versus 31%). A total of 1319 patients (35%) had cirrhosis: 133 GT1a-infected patients (18%); 1074 GT1b-infected patients (41%); 112 GT4-infected patients (25%). In 1469 patients (39%) who had prior treatment experience, 1181 patients (81%) had received pegylated interferon alfa as their most recent prior antiviral treatment; a further 252 patients (17%) had received

TABLE 1 Baseline demographics and clinical characteristics (core population)

| Characteristic | Total N = 3808 |
|---|-------------------|
| Male | 2034 (53) |
| Age, median (range), years | 57 (18-90) |
| >65 years | 871 (23) |
| Race | |
| White/Caucasian | 3375 (89) |
| BMI, mean (SD), kg/m ² | 26.5 (4.7) |
| HCV genotype | |
| 1a | 697 (18) |
| 1a/1b | 11 (<1) |
| 1b | 2618 (69) |
| 1 other/unknown | 25 (<1) |
| 4 | 157 (4) |
| 4 unknown | 300 (8) |
| HCV RNA level, mean (SD), ×10 ⁶ IU/mL | 2.1 (4.7) |
| Human immunodeficiency virus coinfection | 99 (3) |
| Hepatitis B virus coinfection | 53 (1) |
| Cirrhosis status | |
| No cirrhosis | 2011 (53) |
| Transition to cirrhosis | 478 (13) |
| Cirrhosis | 1319 (35) |
| History of liver decompensation | |
| No, never decompensated | 3717 (98) |
| Yes, but currently compensated | 70 (2) |
| Currently decompensated ^a | 20 (<1) |
| Missing, n | 1 |
| Chronic kidney disease | 121 (3) |
| Previous HCV treatment | |
| Naïve | 2339 (61) |
| Experienced | 1469 (39) |
| Comorbidities (≥1) ^b | 2549 (67) |
| Cardiovascular disease | 1184 (31) |
| Diabetes mellitus | 487 (13) |
| Liver and/or CHC-related comorbidities | 477 (13) |
| Psychiatric disorders | 434 (11) |
| Psychoactive substance dependency ^c | 295 (8) |
| Hypothyroidism | 264 (7) |
| Treatment regimen (planned duration) ^d | |
| GT1a ^e (N = 732) | |
| OBV/PTV/r + DSV without RBV (8 weeks) | 1 (<1) |
| OBV/PTV/r + DSV without RBV (12 weeks) | 41 (6) |
| OBV/PTV/r + DSV with RBV (12 weeks) | 654 (89) |
| OBV/PTV/r + DSV with RBV (24 weeks) | 36 (5) |
| GT1b (N = 2619) | |
| OBV/PTV/r + DSV without RBV (8 weeks) | 89 (3) |

(Continues)

TABLE 1 (Continued)

| Characteristic | Total N = 3808 |
|--|-------------------|
| OBV/PTV/r + DSV without RBV (12 weeks) | 1773 (68) |
| OBV/PTV/r + DSV without RBV (24 weeks) | 2 (<1) |
| OBV/PTV/r + DSV without RBV (missing) | 10 (<1) |
| OBV/PTV/r + DSV with RBV (12 weeks) | 737 (28) |
| OBV/PTV/r + DSV with RBV (24 weeks) | 8 (<1) |
| GT4 (N = 457) | |
| OBV/PTV/r with RBV (12 weeks) | 424 (93) |
| OBV/PTV/r with RBV (24 weeks) | 24 (5) |
| OBV/PTV/r + DSV with RBV (12 weeks) | 9 (2) |

Data are n (%) unless stated otherwise. Percentages are based on patients with valid values.

BMI, body mass index; CHC, chronic hepatitis C; DSV, dasabuvir; GT, genotype; HCV, hepatitis C virus; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation.

^aPatients with a Child-Pugh score ≥7 are defined as patients with liver decompensation.

^bComorbidities with prevalence ≥5% included. 975 patients (26%) reported comorbidities that could not be further specified in the electronic case report form.

^cIncluded opioid substitution therapy, n = 235 (6%).

^dPercentages based on total number of patients by HCV genotype.

^eIncludes all GT1 patients except patients with GT1b or GT1b/GT4.

pegylated interferon (not specified), interferon alfa or interferon (not specified). Prior DAA treatment was taken by 162 patients (11%). Regarding current DAA regimens, most patients received 12-week regimens: 654 GT1a-infected patients (89%) received OBV/PTV/r + DSV + RBV; 1773 GT1b-infected patients (68%) received OBV/PTV/r + DSV and 737 GT1b-infected patients (28%) received OBV/PTV/r + DSV + RBV; and 424 GT4-infected patients (93%) received OBV/PTV/r + RBV (Table 1). Overall, 89 GT1b-infected patients (3%) received planned treatment for 8 weeks with OBV/PTV/r + DSV without RBV (fibrosis scores: F0-F1, n = 69 [84%]; F2, n = 11 [13%]; F3, n = 2 [2%]; missing, n = 7; see Table S2B for criteria used to assess overall liver fibrosis stage). Overall, RBV was coadministered to 1892 patients (50%). More than 1 comorbidity was present in 2549 patients (67%; Table 1). The prevalence of renal impairment (according to CTCAE grading) was as follows: 2640 patients (78%) had Grade 0; 409 patients (12%) had Grade 1; 278 patients (8%) had Grade 2; 27 patients (1%) had Grade 3; and 41 patients (1%) had Grade 4 (413 patients had missing data).

3.2 | Virologic response

The overall SVR12 rate in the CPSFU (whole cohort) was 95.9% (n/N = 3401/3546; 95% CI 95.2-96.5). The SVR12 rate was 96.2% (n/N = 3009/3129; 95% CI 95.4-96.8) in GT1-infected patients (GT1a: 92.6% [n/N = 603/651; 95% CI 90.4-94.4]; GT1b: 97.1% [n/N = 2406/2478; 95% CI 96.4-97.7]). The SVR12 rate was 94.0% (n/N = 392/417; 95% CI 91.3-95.9) in GT4-infected patients. SVR12 rates stratified by HCV genotype/subtype and baseline cirrhosis

status are shown in Figure 1A. The overall SVR12 rates in patients with or without cirrhosis were 96% for both subgroups.

SVR12 rates in patients treated according to label-recommended regimens are shown in Figure S4. In patients infected with GT1a treated with OBV/PTV/r + DSV + RBV for planned durations of 12 or 24 weeks, SVR12 rates were 93.3% (n/N = 544/583; 95% CI 91.0-95.1) and 82.4% (n/N = 28/34; 95% CI 66.5-91.7), respectively. In patients infected with GT1b treated with OBV/PTV/r + DSV for planned durations of 8 or 12 weeks, SVR12 rates were 96.3% (n/N = 79/82; 95% CI 89.8-98.7) and 96.7% (n/N = 1600/1654; 95% CI 95.8-97.5), respectively. In patients infected with GT4 treated with OBV/PTV/r + RBV for a planned duration of 12 weeks, SVR12 was 94.0% (n/N = 362/385; 95% CI 91.2-96.0). SVR12 rates in patients who deviated from label-recommended regimens are shown in Figure S5.

In the CPSFU, 145 patients (4.1%) had virologic nonresponse (Table 2). The reasons for nonresponse were as follows: 39 patients (1.1%) had on-treatment virologic failure; 39 patients (1.1%) had post-treatment virologic relapse; 24 patients (<1.0%) died; 30 patients (<1.0%) prematurely discontinued treatment with no on-treatment virologic failure; 13 patients (<1.0%) had insufficient virologic response for other reasons.

In patients with prior HCV treatment experience (Figure 1B), the SVR12 rate was 96.4% (n/N = 1201/1246; 95% CI 95.2-97.3) in GT1-infected patients (GT1a: 91.8% [n/N = 178/194; 95% CI 87.0-94.9; GT1b: 97.2% [n/N = 1023/1052; 95% CI 96.1-98.1]). The SVR12 rate was 92.4% (n/N = 145/157; 95% CI 87.1-95.6) in GT4-infected patients. In HCV treatment-experienced patients, those infected with GT1a with cirrhosis tended to have lower SVR12 rates than patients without cirrhosis, although the number of patients with cirrhosis was comparatively small. Four GT1a-infected patients with cirrhosis had virologic failure, which occurred in two patients at EOT and two patients at the SVR12 visit; a fifth patient prematurely discontinued treatment after 15 days because of an AE and had no post-baseline measurements; and one patient died (this patient had a planned treatment duration of 24 weeks and stopped treatment prematurely on Day 147 due to an AE). SVR12 rates in patients with or without RBV coadministration are shown in Figure 1C and were $\geq 89\%$ irrespective of HCV genotypes/subtypes or cirrhosis status.

In patients with more than 1 comorbidity at baseline, the SVR12 rate was 95.5% (n/N = 2270/2378; 95% CI 94.5-96.2), and 96.8% (n/N = 1131/1168; 95% CI 95.7-97.7) in patients with no comorbidities at baseline. The SVR12 rates ranged from 87.5% to 97.1% across the comorbidity subgroups (Figure 1D). The SVR12 rates in patients with and without renal impairment (according to baseline CrCl) are shown in Figure S6. High SVR12 rates (>92%) were observed in all subgroups except for patients with Grade 3 renal impairment, who had an SVR12 rate of 84% (n/N = 21/25). This subgroup had a relatively small number of patients, of which four patients (GT1b, n = 3; GT4, n = 1) discontinued treatment early because of AEs with no HCV RNA collected after DAA treatment (two patients received RBV).

Overall, 97% of patients in the CPSFU completed the treatment regimen. The overall SVR12 rate was 97.2% in these patients (n/N = 3357/3453; 95% CI 96.6-97.7). In this population, 39 patients (1.1%) had virologic relapse, 31 patients (<1.0%) had on-treatment virologic failure, 13 patients (<1.0%) had insufficient virologic response, and 13 patients (<1.0%) died.

3.3 | Management of comedICATIONS

In the safety population, 58% of patients (n/N = 2237/3850) received ≥ 1 comedication during the treatment period. The most commonly used drug classes (in >5% of patients) were β -blockers (15%; n = 564), analgesics (11%; n = 430), and drugs for peptic ulcers and GERD (10%; n = 394) (Table S3A). The three most commonly used drugs (in $\geq 2\%$ of patients) were levothyroxine (7%; n = 257), acetylsalicylic acid (6%; n = 214) and amlodipine (6%; n = 214) (Table S3B). Based on information available at <https://www.hep-druginteractions.org/>,²¹ none of these commonly used drugs were contraindicated for use with OBV/PTV/r \pm DSV and seven medications had established or potentially clinically relevant DDIs (levothyroxine, amlodipine, bisoprolol, pantoprazole, furosemide, indapamide and omeprazole; Table S3B).

Comedication use was continued for the entire duration of OBV/PTV/r \pm DSV \pm RBV treatment in the majority of patients. Of the patients who took ≥ 1 drug prior to or during DAA treatment, 2116 continued taking ≥ 1 comedication (92%; n/N = 2116/2296), whereas 94 patients permanently discontinued their comedications prior to DAA treatment and 84 discontinued their comedications during DAA treatment (<5% for each). Comedications were discontinued prior to the initiation of OBV/PTV/r \pm DSV \pm RBV treatment and subsequently resumed post-treatment without replacement in 225 patients (10%). Comedications were introduced during the course of DAA treatment in 374 patients (10%). Less than 4% of patients had their comedication replaced (n = 48) or used a substitute drug (n = 47) during OBV/PTV/r \pm DSV \pm RBV treatment.

3.3.1 | Management profiles for specific comedICATIONS

The management profiles for specific comedications that are considered to have a high DDI potential are shown in Figure S7. In the overall population, 417 patients (11%) received drugs for peptic ulcers and GERD, 95 patients (2%) received antiepilepsy drugs, and 90 patients (2%) received antipsychotic drugs prior to or during OBV/PTV/r \pm DSV \pm RBV treatment. The majority of patients (80%-93%; four patients had no profile reported) maintained these comedications without change (ie no comedication discontinuation, replacement, substitution or introduction) throughout DAA treatment (Figure S7). A total of 123 patients (3%) received statin therapy during OBV/PTV/r \pm DSV \pm RBV treatment. Statin therapy (with either rosuvastatin, atorvastatin, pravastatin or simvastatin) was maintained without change in 53 patients (43%); 46 (37%) discontinued statin therapy before DAA treatment and subsequently resumed

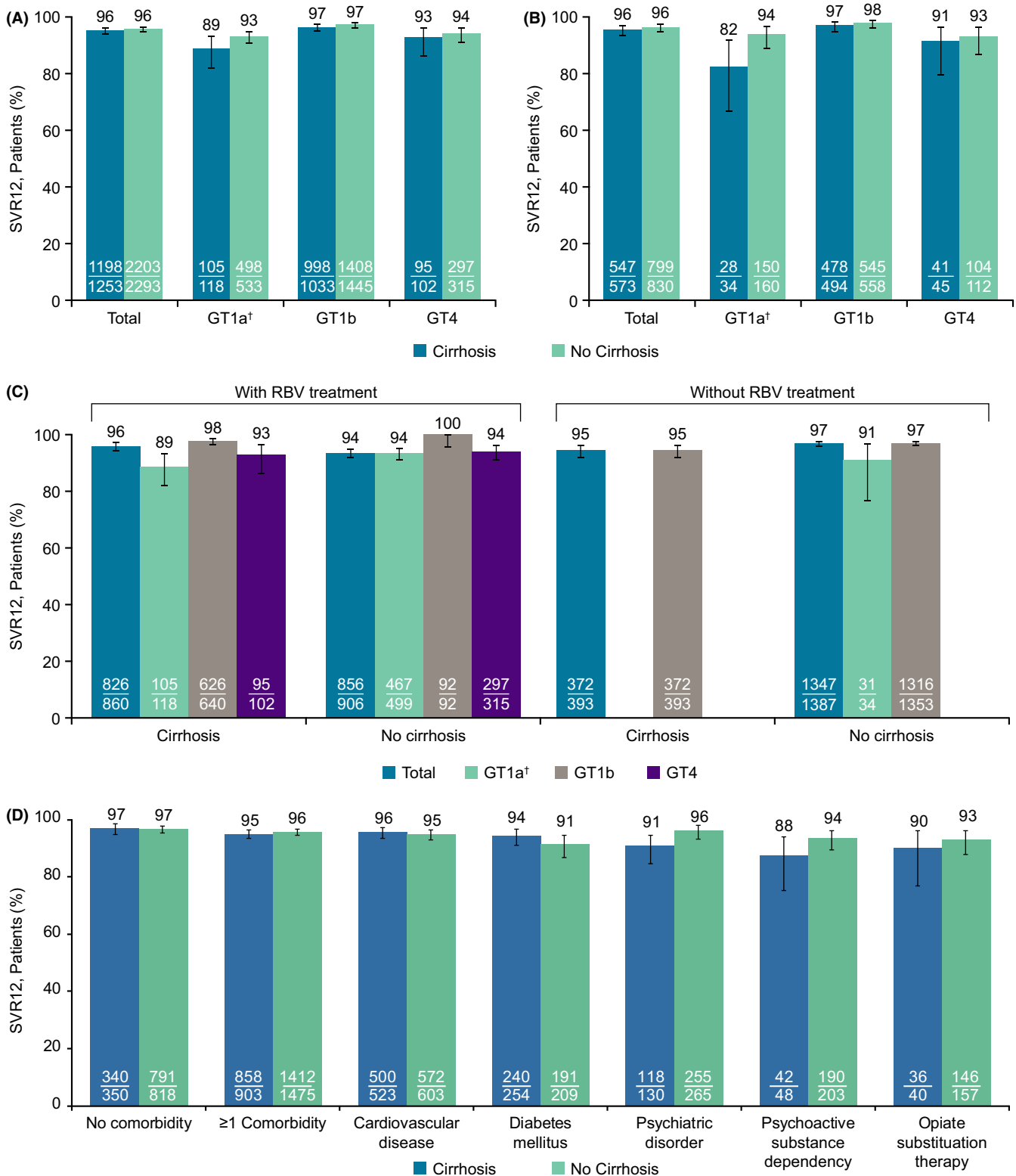


FIGURE 1 SVR12 rates by HCV genotype/subtype and cirrhosis status in (A) the overall population, (B) patients with prior treatment experience, (C) by ribavirin treatment (CPSFU population) and (D) by baseline comorbidity subgroups. Error bars represent 95% confidence intervals. †Patients infected with GT1a include those with other/unknown subtypes except G1b. CPSFU, core population with sufficient follow-up; GT, genotype; HCV, hepatitis C virus; RBV, ribavirin; SVR12, sustained virologic response at post-treatment Week 12

post-treatment (without replacement); and 17 (14%) permanently discontinued statin therapy before or during DAA treatment (without replacement).

The SVR12 rates in patients with confirmed use of drugs for peptic ulcers and GERD, statins, antipsychotics or antiepileptics during OBV/PTV/r ± DSV ± RBV treatment versus those who had never

TABLE 2 Virologic nonresponse rates by HCV genotype/subtype and cirrhosis status (CPSFU population)

| | Total N = 3546 | | GT1a ^a N = 651 | | GT1b N = 2478 | | GT4 N = 417 | |
|---|-----------------------|--------------------------|------------------------------|-------------------------|-----------------------|--------------------------|----------------------|-------------------------|
| | Cirrhosis N = 1253 | No cirrhosis N = 2293 | Cirrhosis N = 118 | No cirrhosis N = 533 | Cirrhosis N = 1033 | No cirrhosis N = 1445 | Cirrhosis N = 102 | No cirrhosis N = 315 |
| Overall | 55 (4) | 90 (4) | 13 (11) | 35 (7) | 35 (3) | 37 (3) | 7 (7) | 18 (6) |
| On-treatment virologic failure ^b | 13 (1) | 26 (1) | 3 (3) | 9 (2) | 7 (<1) | 8 (<1) | 3 (3) | 9 (3) |
| Relapse ^c | 11 (<1) | 28 (1) | 1 (<1) | 14 (3) | 9 (<1) | 10 (<1) | 1 (1) | 4 (1) |
| Death | 13 (1) | 11 (<1) | 2 (2) | 3 (<1) | 10 (1) | 7 (<1) | 1 (1) | 1 (<1) |
| Premature study drug discontinuation ^d | 13 (1) | 17 (<1) | 5 (4) | 4 (<1) | 7 (<1) | 10 (1) | 1 (1) | 3 (1) |
| Insufficient virologic response reported (other reasons) ^e | 5 (<1) | 8 (<1) | 2 (2) | 5 (<1) | 2 (<1) | 2 (<1) | 1 (1) | 1 (<1) |

CPSFU, core population with sufficient follow-up; EOT, end of treatment; GT, genotype; HCV, hepatitis C virus; RNA, ribonucleic acid.

^aPatients infected with GT1a include those with other/unknown subtypes except G1b.

^bBreakthrough (defined as at least 1 documented HCV RNA measurement <50 IU/mL followed by an HCV RNA measurement ≥50 IU/mL during treatment) or failure to suppress (each on-treatment HCV RNA measurement ≥50 IU/mL).

^cDefined as an HCV RNA measurement <50 IU/mL at EOT followed by an HCV RNA measurement ≥50 IU/mL post-treatment in patients who completed treatment (not more than 7 days shortened).

^dWith no on-treatment virologic failure.

^ePatients for whom insufficient virologic response was reported, or who had an HCV RNA measurement ≥50 IU/mL post-EOT and none of the above.

used these drugs before or during OBV/PTV/r ± DSV ± RBV treatment are shown in Figure S8. The SVR12 rates in patients who used these drug classes ranged from 90% to 95%. The SVR rate in patients who did not use the respective drug class was 96% in each case.

3.4 | Safety

In the safety population (N = 3850), 1008 patients (26.2%) reported ≥1 treatment-emergent AE (Table 3). The most common AEs were fatigue (n = 246; 6.4%) and anaemia (n = 202; 5.2%). Treatment-emergent serious AEs occurred in 129 patients (3.4%), with anaemia (n = 15; 0.4%), hepatic failure (n = 7; 0.2%), hepatocellular carcinoma (n = 5; 0.1%) and jaundice (n = 4; 0.1%) being the most frequently reported serious AEs. The incidence of anaemia was most frequently reported in patients who received RBV.

The total number of deaths reported was 32. Treatment-emergent AEs leading to death occurred in 14 patients. The AEs reported for these patients were cardiac failure (n = 1), cardiopulmonary failure (n = 1), myocardial infarction (n = 1), gastrointestinal haemorrhage (n = 1), oesophageal variceal haemorrhage (n = 1), decompensated liver cirrhosis (n = 1), hepatic failure (n = 1), acute pyonephrosis (n = 1; renal abscess), sepsis (n = 1; thoracic wall abscess due to immunosuppression), overdose (n = 2; 1 patient had substance overdose; 1 patient had methadone overdose), carotid aneurysm rupture (n = 1), sudden death (n = 1) and chronic kidney disease (n = 2).

In patients who received drugs for peptic ulcers and GERD, antiepilepsy drugs, antipsychotic drugs or statins, ≥1 AE was reported by 24%–26% of patients who had never used these drugs before or during OBV/PTV/r ± DSV ± RBV treatment, and by 39%–47% of

patients with confirmed use of these drugs during DAA treatment (Table S4). The most common AEs (in ≥5% of patients) were anaemia and fatigue, which occurred more frequently in patients with confirmed use of drugs for peptic ulcers and GERD, statins, and antipsychotics. The rates of these AEs were similar between patients using and not using antiepileptic drugs.

The incidence of post-baseline Grade 3 or higher laboratory abnormalities reported was infrequent. In the overall population, Grade 3 and 4 elevations in ALT levels occurred in 15 patients (1.5%) and 2 patients (<1.0%), respectively. Grade 3 elevations in AST levels occurred in 6 patients (<1.0%); no Grade 4 elevations were observed. Grade 3 and 4 decreases in haemoglobin levels occurred in 17 patients (<1.0%) and 1 patient (<1.0%), respectively. Grade 3 and 4 decreases in CrCl occurred in 30 patients (1.1%) and 37 patients (1.3%), respectively. A summary of laboratory abnormalities by treatment regimen is shown in Table S5.

The mean (standard deviation [SD]) treatment duration of OBV/PTV/r ± DSV ± RBV regimens was 84 (15) days. Overall, 120 patients (3.1%) prematurely discontinued these regimens; the reasons for discontinuation included AEs or serious AEs (54 patients; 1.4%), patient refusal to continue treatment (22 patients; <1.0%), consent withdrawal or lost to follow-up (18 patients; <1.0%), viral relapse or breakthrough (two patients; <1.0%) and other nonsafety-related reasons (24 patients; <1.0%). The mean (SD) duration of RBV treatment was 83 (21) days. Treatment with RBV was discontinued before termination of the OBV/PTV/r ± DSV regimens in 94 patients (5.0%). The reasons for RBV discontinuation were anaemia (39 patients; 2.1%), rash (seven patients; <1.0%), nausea/vomiting (seven patients; <1.0%) and other reasons (41 patients; 2.2%).

TABLE 3 Summary of treatment-emergent AEs by treatment regimen (safety population)

| Adverse event | OBV/PTV/r N = 20 | | OBV/PTV/r + RBV N = 455 | | OBV/PTV/r + DSV N = 1930 | | OBV/PTV/r + DSV + RBV N = 1445 | |
|--|---------------------|------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|-----------------------------------|-------------------------|
| | Cirrhosis N = 2 | No cirrhosis N = 18 | Cirrhosis N = 114 | No cirrhosis N = 341 | Cirrhosis N = 433 | No cirrhosis N = 1495 | Cirrhosis N = 785 | No cirrhosis N = 660 |
| At least 1 AE | 2 (100) | 4 (22) | 37 (32) | 96 (28) | 103 (24) | 331 (22) | 209 (27) | 225 (34) |
| Serious AEs | 0 | 0 | 8 (7) | 6 (2) | 24 (6) | 28 (2) | 40 (5) | 23 (3) |
| AEs leading to death | 0 | 0 | 1 (<1) | 0 | 2 (<1) | 1 (<1) | 6 (<1) | 4 (<1) |
| Common AEs (in ≥5% of patients) ^a | | | | | | | | |
| Anaemia | 0 | 0 | 18 (16) | 28 (8) | 1 (<1) | 2 (<1) | 95 (12) | 58 (9) |
| Fatigue | 0 | 1 (6) | 8 (7) | 22 (6) | 17 (4) | 103 (7) | 28 (4) | 67 (10) |

Data are n (%). AEs with onset between treatment initiation and end of treatment (or treatment initiation plus planned treatment duration when treatment end was missing) plus 30 days post-treatment, including AEs with missing onset date and treatment-related AEs irrespective of onset.

AE, adverse event; DSV, dasabuvir; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin.

^aAt the preferred term level; ≥5% of patients in the total safety population (N = 3850).

4 | DISCUSSION

This pooled analysis of patient-level data from post-marketing observational studies was conducted to evaluate the safety and effectiveness of OBV/PTV/r ± DSV ± RBV, including the impact of common comorbidities and comedications, when used in daily clinical practice and in accordance with local guidelines and label recommendations. The results provide real-world evidence that these regimens are highly effective in patients infected with HCV GT1 or GT4. The SVR12 rate was 96% across the entire cohort, which complements the high efficacy reported in pivotal clinical trials.⁷⁻¹² Similarly, rates of on-treatment virologic failure and post-treatment relapse (2.2%) compare favourably with those reported in clinical trials.^{7-12,22} Common comorbidities had minimal impact on the effectiveness of OBV/PTV/r ± DSV ± RBV, and most patients continued taking their comedications during treatment.

Overall, SVR rates remained high regardless of cirrhosis status, prior HCV treatment experience or RBV coadministration. GT1a-infected patients with cirrhosis had lower SVR12 rates compared with other subgroups. One explanation for this finding is that GT1a-infected patients with compensated cirrhosis are eligible for a 12-week regimen depending on their virologic response to previous peginterferon-based treatment, despite the recommended treatment duration of 24 weeks.¹⁻³ However, in clinical trials, lower SVR12 rates in GT1a-infected patients with prior null response or relapse to previous HCV treatment were observed with 12 versus 24 weeks of OBV/PTV/r + DSV + RBV treatment.¹¹ In GT1b-infected patients, SVR12 rates were not significantly impacted by cirrhosis status, prior treatment experience or a shorter 8-week treatment regimen. These trends in SVR12 rates are consistent with those seen in pivotal clinical trials.^{7-9,11,12,20} Similarly, in GT4-infected patients, SVR12 rates compared favourably with those seen in clinical trials (94%-100%).^{10,23,24}

As expected, most patients had ≥1 comorbidity and SVR12 rates were numerically similar between patients with versus

without comorbidities (95% vs 97%). SVR12 rates ranged from 88% to 97% across all evaluated comorbidity subgroups, suggesting comorbidities had minimal impact on the effectiveness of OBV/PTV/r ± DSV ± RBV. Clinically relevant subgroups such as patients receiving opioid substitution therapy or with psychiatric disorders have faced significant barriers to HCV therapy because of concerns regarding poor adherence to treatment, HCV reinfection and AEs.²⁵ The recent availability of highly effective DAA therapies and integrated approaches to care management have increased the rates of successful HCV treatment in these populations.²⁶ In this analysis, SVR12 rates in these subgroups were comparable to the overall population. This was also true for patients with renal impairment, consistent with the clinical trial results²⁷ and other real-world studies.^{9,28}

As a result of the high prevalence of comorbid conditions in HCV-infected patients, comedications are frequently prescribed, many of which have the potential to interact with DAA drugs.^{17,29} DDIs can negatively impact a drug's therapeutic efficacy and therefore have important implications for routine clinical care. All recently approved DAA therapies interact with drug-metabolizing enzymes or drug transporters. Careful pretreatment screening for potential DDIs, using resources such as the University of Liverpool website (www.hep-druginteractions.org),²¹ can help guide clinicians prescribe the most appropriate regimen. HCV treatment guidance recommends all patients are assessed for comorbidities and potential DDIs before undergoing DAA treatment, and before starting other comedications during DAA treatment.^{5,6} OBV/PTV/r ± DSV-based regimens are contraindicated for coadministration with drugs that are highly dependent on CYP3A for clearance, strong inducers of CYP3A and CYP2C8, and strong inhibitors of CYP2C8.¹⁻⁴

Studies in large real-world cohorts have shown that a significant number of patients receiving comedications and treated with OBV/PTV/r ± DSV ± RBV are potentially at risk for DDIs.^{17,29} In the present study, more than half of the patients (58%) received

≥1 comedication during the treatment period. None of the most commonly used comedications were contraindicated, although 7 had clinically relevant DDIs. Nevertheless, >90% of patients taking comedications continued to receive at least 1 of their drugs during treatment. We specifically evaluated the treatment profiles of drugs for peptic ulcers and GERD, statins, antiepileptics and antipsychotics because these drug classes include several medications that are either contraindicated and/or have established DDIs with OBV/PTV/r ± DSV and are therefore considered more difficult to manage. Although AE rates were higher in patients who had confirmed use of these drug classes during OBV/PTV/r ± DSV ± RBV treatment versus those who had never used these drugs before or during DAA treatment, most patients continued to receive these comedications throughout DAA treatment, with appropriate adjustments made to their management. Consistent with their widespread use in the general population, drugs for peptic ulcers and GERD were frequently used in this population (10% of patients). Furthermore, despite the established DDI between omeprazole and OBV/PTV/r ± DSV, which results in a decrease in omeprazole concentration (but no effect on DAA component concentrations),¹ most patients maintained this comedication class without change, and the SVR12 rate remained at 95%, suggesting that acid-related symptoms were well controlled. Overall, the use of statins, antipsychotics or antiepileptics was low in this patient cohort (≤3% for each class) and their use was associated with small decreases in SVR12 rates versus patients who did not use these drugs before or during DAA treatment (90%–92% vs 96%). However, more than half of the patients taking statins required adjustments before or during OBV/PTV/r ± DSV ± RBV treatment. These adjustments are consistent with drug labelling for OBV/PTV/r ± DSV, which stipulates that members of the statin class are either contraindicated (lovastatin, atorvastatin and simvastatin) or should be used at reduced doses (rosuvastatin and pravastatin) because of possible DDIs leading to increases in statin concentrations and the potential for myopathy.^{1–4} The antipsychotic and antiepileptic classes also include several drugs that are contraindicated with OBV/PTV/r ± DSV. The antiepileptic drugs carbamazepine, phenytoin and phenobarbital may decrease exposures of OBV, PTV, DSV and ritonavir (via CYP3A4 induction), leading to a potential loss in anti-HCV therapeutic activity and therefore must not be coadministered.^{1–4} Exposures to the antipsychotic drugs lurasidone, pimozone or quetiapine may be increased when coadministered with OBV/PTV/r ± DSV (via CYP3A4 inhibition by ritonavir), potentially leading to serious or life-threatening adverse reactions.^{1–4} Overall, however, more than 80% of patients continued to receive each drug class without change to their management.

The overall incidence of treatment-emergent AEs (26%) was considerably lower than that seen in pivotal clinical trials of OBV/PTV/r ± DSV-based regimens (67%–92%), suggesting that safety outcomes may have been underreported in this real-world study. The incidence of serious AEs (3%) was consistent with rates reported in clinical trials.^{7–12} No new or unexpected AEs were observed, and fatigue and anaemia were the only AEs that occurred in >5% of the overall population. As expected, the incidence of

anaemia was more frequent in patients who received RBV in the present study and was the main reason for patients discontinuing RBV treatment before terminating OBV/PTV/r ± DSV + RBV regimens. Low rates (3.1%) of DAA drug discontinuation were observed, consistent with the rates in clinical trials. Similarly, the incidence of laboratory abnormalities was largely in accordance with that seen in clinical trials.^{7–12}

The number of large real-world studies of OBV/PTV/r ± DSV ± RBV regimens in routine clinical practice is currently limited. Clinical practice data from the German Hepatitis C Registry, which included 558 patients treated with OBV/PTV/r ± DSV ± RBV, showed that SVR12 rates were 96% in GT1- and 100% in GT4-infected patients, regardless of cirrhosis status or prior antiviral treatment.³⁰ The incidence of AEs and serious AEs were 52% and 2%, respectively. A meta-analysis of real-world data from 5726 patients receiving OBV/PTV/r ± DSV-based regimens showed that 5548 patients achieved SVR12 (97%), regardless of cirrhosis status.³¹ The rate of discontinuations attributable to AEs was ≤3%, and the incidence of serious AEs was ≤5%. Another similar meta-analysis of real-world data from 5158 OBV/PTV/r ± DSV ± RBV-treated patients (20 cohorts from 12 countries) reported SVR12 rates of ≥94% in HCV GT1- or GT4-infected patients.³² SVR12 rates in patients with or without cirrhosis and by prior antiviral treatment were generally similar across HCV genotypes/subtypes. An analysis of 150 treatment-naïve patients from the Spanish Hepa-C registry who were infected with GT1b and treated with OBV/PTV/r + DSV for 8 weeks showed high SVR12 rates (97%), with no serious AEs or treatment discontinuations reported.³³ Large real-world effectiveness studies from the US Veterans' Affairs National Health Care System have reported overall SVR12 rates in the range 86%–95% in GT1-infected patients treated with OBV/PTV/r ± DSV-based regimens, which is approaching the rate seen in clinical trials.^{34–36} Lower SVR12 rates in this US Veteran population are not unexpected because these patients tend to have a high prevalence of comorbidities that have historically been considered difficult to treat. Other real-world studies of OBV/PTV/r ± DSV-based regimens have shown SVR12 rates that are equivalent to the rates seen in clinical trials.^{37–39} Taken together, our results support the accumulating body of real-world evidence confirming the safety and effectiveness of OBV/PTV/r ± DSV ± RBV regimens in routine clinical practice.

This analysis has several limitations. As with any real-world study, there is scope for considerable bias in the reporting and collection of patient-level information. In particular, safety outcomes are often limited by underreporting in the real-world setting. Additionally, DDI screening prior to the initiation of antiviral treatment will often predicate the choice of DAA drug based on comedication usage. Nevertheless, we observed comedication class usage typical of the comorbidities seen in this real-world cohort. The reasons for changes in comedication management were not reported; therefore, it was not determined whether adjustments in comedications were as a result of DDIs. A further limitation was that information regarding comedication dose modification or temporary interruption was not documented in patients who were classified as having continuous comedication treatment. It was also not possible to establish a relationship between

DDIs and AEs. Finally, some subgroups in this analysis had comparatively small patient numbers, and therefore, meaningful conclusions on safety and effectiveness cannot be inferred using these subgroups.

Although several new pangenotypic DAA regimens are now approved for the treatment of chronic HCV infection, access is still limited for many countries.⁴⁰ Until such access is achieved, genotype-specific DAAs such as OBV/PTV/r ± DSV ± RBV remain the standard of care treatment for patients with chronic HCV infection. This analysis of real-world data from a large cohort of diverse patients provides evidence that in daily clinical practice, OBV/PTV/r ± DSV ± RBV regimens are effective treatment options for patients with chronic HCV GT1 or GT4 infection, including those with diverse comorbidity and comedication profiles. As with other real-world studies, safety outcomes may be limited by underreporting of AEs. The high degree of concordance observed between our real-world data, and the results from pivotal clinical trials suggests that the reported efficacy of OBV/PTV/r ± DSV ± RBV regimens in clinical trials translates to routine clinical practice.

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AUTHOR CONTRIBUTION

All authors had access to all relevant data and participated in the writing, review, and approval of this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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