# Common Drug Review
## *Clinical Review Report*

**May 2016**

| | |
|---|---|
| **Drug** | Elbasvir/Grazoprevir (Zepatier) |
| **Indication** | For the treatment of chronic hepatitis C (CHC) genotypes 1, 3, or 4 infection in adults as follows:<br>Without ribavirin:<br>• in genotype (GT) 1 or 4 treatment-naive (TN) and peginterferon alfa + ribavirin (PR) treatment-experienced (TE) relapsers (12 weeks)<br>• in GT1 protease inhibitor (PI)/PR-TE relapsers (12 weeks)<br>• in GT1b TN, non-cirrhotic patients (8 weeks)<br>• in GT1b PR- or PI/PR-TE on-treatment virologic failures (12 weeks)<br>With ribavirin:<br>• in GT1a PR- or PI/PR-TE on-treatment virologic failures (16 weeks)<br>• in GT4 PR-TE on-treatment virologic failures (16 weeks)<br>With sofosbuvir:<br>• in GT3 TN patients (12 weeks) |
| **Reimbursement request** | As per indication |
| **Dosage form(s)** | Elbasvir/Grazoprevir in a single tablet (50/100 mg) for oral administration |
| **NOC date** | 19 January 2016 |
| **Manufacturer** | Merck Canada Inc. |

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

# TABLE OF CONTENTS



**Tables**

**Figures**

# ABBREVIATIONS

| | |
|---|---|
| **AE** | adverse event |
| **CI** | confidence interval |
| **CHC** | chronic hepatitis C |
| **CKD** | chronic kidney disease |
| **CLDQ-HCV** | HCV-specific version of the Chronic Liver Disease Questionnaire |
| **CrCl** | creatinine clearance |
| **DB** | double-blind |
| **DAA** | direct-acting antiviral agent |
| **EBR** | elbasvir |
| **EQ-5D** | EuroQoL 5-Dimensions Health-Related Quality of Life Questionnaire |
| **EQ VAS** | EuroQol Visual Analogue Scale |
| **FACIT** | Functional Assessment of Chronic Illness Therapy |
| **FAS** | full analysis set |
| **FDA** | US Food and Drug Administration |
| **FDC** | fixed dose combination |
| **GT** | genotype |
| **GZR** | grazoprevir |
| **HCV** | hepatitis C virus |
| **HRQoL** | health-related quality of life |
| **LOCF** | last observation carried forward |
| **MCID** | minimal clinically important difference |
| **MCS** | mental component summary |
| **mFAS** | modified full analysis set |
| **PCS** | physical component summary |
| **PK** | pharmacokinetic(s) |
| **PP** | per-protocol |
| **PR** | pegylated interferon plus ribavirin |
| **RBV** | ribavirin |
| **RCT** | randomized controlled trial |
| **SAE** | serious adverse event |
| **SD** | standard deviation |
| **SF-36** | Short Form 36-Item Health Survey |
| **SOF** | sofosbuvir |
| **SVR** | sustained virologic response |
| **WDAE** | withdrawal due to adverse event |
| **WPAI** | Work Productivity and Activity Impairment questionnaire |

# EXECUTIVE SUMMARY

## Introduction

In 2013, an estimated 250,000 Canadians had chronic hepatitis C (CHC) virus infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[1] There are six major hepatitis C virus (HCV) genotypes, of which genotype 1 infections are the most common in Canada (~65%).[1] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada.[1] Genotype 4 is less common in Canada and accounts for less than 1% of HCV cases.[1] Hepatitis C most commonly affects people older than 30 years, and disproportionately men.[2] Other populations at higher risk for HCV infection include federal inmates, men who have sex with men, street-involved youth, and Aboriginal peoples.[2] Of those with chronic infection, 15% to 25% will develop progressive liver disease, end-stage liver disease, or hepatocellular carcinoma, or will require liver transplant.[3] It is expected that liver-related morbidity and mortality will increase over the coming decades, as those who are already infected age.[1,4-7] Patients have expressed the need for affordable and accessible new treatments with higher cure rates, better side effect profiles, and reduced treatment burden, particularly for those with genotypes 3 and 4 CHC.

The treatment paradigm for hepatitis C has been shifting rapidly as evidence emerges and new direct-acting antiviral agents (DAAs) come onto the market. A number of interferon-free DAA regimens have recently been approved in Canada for CHC genotypes 1 to 4, with improved tolerability, high response rates, and shorter treatment durations than the previous interferon-based treatment regimens.[8] Zepatier is a combination of elbasvir (EBR) and grazoprevir (GZR). The objective of this systematic review was to evaluate the beneficial and harmful effects of EBR/GZR alone or in in combination with other drugs for genotypes 1, 3, and 4 CHC.

| **Indication under review** |
|---|
| Alone or in combination with other agents for the treatment of chronic hepatitis C (CHC) genotypes 1, 3, or 4 infection in adults |
| **Reimbursement criteria requested by sponsor** |
| As per indication |

## Results and Interpretation

### Included Studies

A total of eight trials met the inclusion criteria for this systematic review. Two trials were randomized, double-blinded placebo-controlled trials (C-EDGE Treatment-Naive [N = 421], and C-SURFER [N = 237]); three trials were randomized, parallel-group, open-label trials (C-EDGE Treatment-Experienced [420], C-SWIFT [143], and C-WORTHY [573]); and three were open-label, non-randomized trials (C-EDGE Coinfection [N = 218], C-SALVAGE [N = 79], and C-SCAPE [N = 98]). The trials evaluated 12-week treatment with EBR/GZR alone (C-EDGE Treatment-Naive, C-SURFER, C-EDGE Coinfection, and C-SCAPE), eight-week or 12-week treatment with EBR/GZR alone (C-WORTHY), 12-week treatment with EBR/GZR plus ribavirin (RBV) (C-SALVAGE), 12-week treatment with EBR/GZR or 16-week treatment with EBR/GZR plus ribavirin (C-EDGE Treatment-Experienced), or 12-week treatment with EBR/GZR plus sofosbuvir (SOF) (C-SWIFT). The trials enrolled adults with CHC genotypes 1, 4, or 6 (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-EDGE Treatment-Experienced), genotype 1 (C-SURFER, C-SALVAGE), genotypes 1 or 3 (C-SWIFT, C-WORTHY), or genotypes 2, 4, 5 or 6 (C-SCAPE). Four trials enrolled patients who were

treatment-naive (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SWIFT, C-SCAPE); two trials included treatment-experienced patients (C-EDGE Treatment-Experienced, C-SALVAGE); and two trials included treatment-naive and treatment-experienced patients (C-SURFER, C-WORTHY). In the C-EDGE Treatment-Experienced study, the treatment-experienced patients had a prior null, partial response or relapse to pegylated interferon plus ribavirin (PR), while in the C-SALVAGE study, the treatment-experienced patients had prior non-response, breakthrough, or relapse to PR + DAA. The treatment-experienced patients in the C-SURFER study had prior interferon or PR treatment failures, null response, partial response, or relapse. Patients included in the C-EDGE Coinfection study had to be coinfected with HIV, and patients included in the C-SURFER study had to have chronic kidney disease (CKD).

The main outcome in the included trials was the proportion of patients achieving sustained virologic response at 12 weeks (SVR12). In the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, and C-EDGE Treatment-Experienced trials, the SVR12 rate was compared with a historical comparison base rate from simeprevir plus PR, sofosbuvir plus RBV, PR, and simeprevir plus PR, respectively. The historical control rates used were 73%, 70%, 45%, and 58% in the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, and C-EDGE Treatment-Experienced trials, respectively. Other outcomes included relapse rate and health-related quality of life (HRQoL).

The main limitation of the included trials was the lack of an active treatment comparator arm consisting of an existing treatment regimen for CHC genotype 1, 3, or 4 infection. Comparison with a historical control could be biased due to differences in the distribution of potential confounders of effect and because the trials from which the historical control rates were derived were conducted at a different time, with potential differences in the standard of care at that time. Despite the scientific limitations associated with historical control study designs, these designs were considered adequate by Health Canada and the FDA to grant regulatory approval. Limited data were available in patients with genotype 3 and 4 CHC.

**Efficacy**

In the C-EDGE Treatment-Naive study, the SVR12 rate was 95% (95% confidence interval [CI], 92% to 97%) in the treatment-naive genotype 1, 4, or 6 CHC patients who received EBR/GZR for 12 weeks. The lower bound of the 95% CI (92%) exceeded the 73% historical control rate for simeprevir plus PR that was specified as the primary objective. In the C-EDGE Coinfection study, the SVR12 rate was 95% (95% CI, 91% to 98%) in the treatment-naive genotype 1, 4, or 6 CHC patients who were coinfected with HIV and received EBR/GZR for 12 weeks. The lower bound of the 95% CI (91%) exceeded the 70% historical control rate for sofosbuvir plus RBV that was specified as the primary objective. In the C-SURFER study, the SVR12 rate using the modified full analysis set population was 99% (95% CI, 95% to 100%) in the treatment-naive or treatment-experienced genotype 1 CHC patients who had CKD and received EBR/GZR for 12 weeks. The lower bound of the 95% CI (95%) exceeded the 45% reference SVR rate that was specified as the primary objective. The SVR rate in the C-SURFER trial using the full analysis set population was 94% (95% CI, 89% to 98%). In the C-EDGE Treatment-Experienced study, the SVR12 rates were 92% (95% CI, 86% to 97%), and 97% (95% CI, 92% to 99%) in the treatment-experienced genotype 1, 4, or 6 CHC patients who received EBR/GZR for 12 weeks and EBR/GZR + RBV for 16 weeks, respectively. The lower bound of the 95% CI (86% and 92%) exceeded the 58% historical control rate for simeprevir plus PR that was specified as the primary objective.

Overall, EBR/GZR for 12 weeks achieved SVR12 rates between 90% and 100% among patients with genotype 1 CHC, and showed similar response rates regardless of the patients' prior treatment history, genotype subtype, presence of CKD, or presence of cirrhosis. EBR/GZR for 12 weeks also achieved SVR12

rates between 87% and 96% among treatment-naive patients with genotype 1 CHC who are coinfected with HIV (C-EDGE Coinfection, and C-WORTHY trials). EBR/GZR for eight weeks achieved SVR12 rates of 97% among treatment-naive patients with genotype 1b CHC with METAVIR fibrosis scores of F0 to F2 (C-WORTHY trial). Among patients experienced to PR who received EBR/GZR + RBV for 16 weeks, an SVR rate of 95% was reported for genotype 1a, while in those with genotype 1b, a SVR rate of 100% was achieved (C-EDGE Treatment-Experienced trial). Patients with prior treatment experience with DAA who received EBR/GZR + RBV for 12 weeks had a response rate of 96% in patients with genotype 1a and 98% among patients with genotype 1b (C-SALVAGE trial).

Among treatment-naive patients with genotype 4 who received EBR/GZR for 12 weeks, SVR12 ranged from 90% to 100% (9/10 [90%] in the C-SCAPE trial, 18/18 [100%] in the C-EDGE Treatment-Naive trial, and 27/28 [96.4%] in the C-EDGE Coinfection trial), while in those who were treatment-experienced, the SVR rate was 78% (7/9 [77.8%] in the C-EDGE Treatment-Experienced trial). Treatment-experienced patients with genotype 4 who received EBR/GZR + RBV for 16 weeks achieved an SVR rate of 100% (8/8 [100%] in the C-EDGE Treatment-Experienced trial). The number of patients with genotype 4 included in the trials was limited; hence, the generalizability of the results is unclear. In addition, the characteristics of the study population were not reported by genotype, and therefore we are not sure if the patient population with genotype 4 is representative of or similar to the population with genotype 4 in Canada.

Only the C-SWIFT trial included patients with genotype 3. Treatment-naive non-cirrhotic patients with genotype 3 who received EBR/GZR + SOF for 12 weeks had a response rate of 100%, while cirrhotic patients had a response rate of 83%; however, the number of patients included was limited (14 non-cirrhotic and 12 cirrhotic patients), and the generalizability of the results is therefore uncertain.

The included trials reported few cases of relapse. The reported relapses could be associated to the existence of nonstructural protein 5A (NS5A) polymorphisms, where in the C-EDGE Treatment-Naive trial, among the 10 genotype 1a–infected patients who experienced virologic failure, nine (90%) had treatment-emergent NS5A resistance-associated variants (RAVs) at failure. In the single genotype 1b–infected patient who experienced virologic failure, a treatment-emergent NS5A RAV was detected at failure. Also in the C-EDGE Coinfection trial, the four relapsed patients were assessed for treatment-emergent mutations and it was found that two patients had NS3 and three had NS5A. The presence of specific NS5A RAVs in genotype 1a patients is associated with a more than five-fold decrease in EBR *in vitro* antiviral activity, and may explain the reduced efficacy observed in this subset of patients. For example, results were 2/9 (22.2%) in the C-EDGE Treatment-Naive trial, 3/4 (75.0%) in the C-EDGE Coinfection trial, and 6/6 (100%) in the C-SURFER trial in treatment-naive patients who received EBR/GZR for 12 weeks, 2/6 (33.3%) in the C-EDGE Treatment-Experienced trial in treatment-experienced patients who received EBR/GZR for 12 weeks, and 0/1 (0%) in the C-SALVAGE trial in treatment-experienced patients who received EBR/GZR + RBV for 12 weeks.

Patient group input emphasized the impact that chronic hepatitis infection has on patients' quality of life. HRQoL was measured using the Short Form 36-Item Health Survey (SF-36), EuroQol Visual Analogue Scale (EQ VAS), and HCV-specific version of the Chronic Liver Disease Questionnaire (CLDQ-HCV) in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials. Other patient-reported outcomes (PROs) in these trials included the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) Scale and the Work Productivity and Activity Impairment questionnaire (WPAI). HRQoL was also measured using the SF-36 and EQ VAS scores in the C-SURFER trial. Across the different PROs, the mean change from baseline in PRO scores during treatment and follow-up did not appreciably differ between EBR/GZR and placebo, whereas in the C-EDGE Treatment-Naive trial, there was no statistically

significant difference between EBR/GZR and placebo groups in the vitality, general health, role physical and role emotional domains, and the physical component summary (PCS) of the SF-36, EQ-5D VAS scores, Overall CLDQ-HCV, the FACIT-F Scale, and the WPAI. In the C-SURFER trial, the mean changes from baseline in HRQoL scores at treatment week 12 did not differ between the GZR + EBR and placebo groups for vitality, general health, role physical, role emotional, mental component summary (MCS), and PCS of the SF-36. The addition of RBV to EBR/GZR did contribute to a worsening of HRQoL, fatigue levels, and work productivity and activity impairment during treatment. Better HRQoL, less fatigue, and less work productivity and activity impairment for EBR/GZR groups were found when compared with the EBR/GZR + RBV groups during the treatment period. At follow-up week 12, HRQoL, fatigue, and work productivity and activity impairment scores were near or better than the baseline scores in patients treated with EBR/GZR plus RBV. It should be noted that most values, particularly those in RBV-free arms, did not deteriorate through treatment, unlike what is typically seen with HRQoL scores from other DAA-based regimens that include PR.[9] Finally, it is worth noting that PROs were exploratory efficacy end points and no formal hypothesis testing was applied.

Despite the absence of direct comparative trials of EBR/GZR with other treatments for CHC infection, no indirect comparisons were submitted by the manufacturer or identified in the literature.

**Harms**

Adverse events (AEs) were frequent across all treatment groups in the included trials, ranging from 53.3% to 91.7% for patients on EBR/GZR for 12 weeks, 54.8% among those who received EBR/GZR for eight weeks, 79.7% among those who received EBR/GZR + RBV for 12 weeks, 89.6% among those who received EBR/GZR + RBV for 16 weeks, and from 21.4% to 33.3% among those who received EBR/GZR plus sofosbuvir for 12 weeks. The frequency of AEs in patients who received placebo ranged from 68.6% to 84.1%. In the C-EDGE Treatment-Naive trial, EBR/GZR was generally well tolerated, with a similar safety profile in the active and placebo treatment groups. Serious AEs were rare, with similar frequencies in the active and placebo groups. Discontinuations for AEs were likewise uncommon. The most common AEs were headache, fatigue, and nausea, with similar frequencies in the active and placebo arms. In the C-SURFER trial in which patients had to have CKD, EBR/GZR was generally well tolerated in the CKD patient population. Overall, the safety profiles of patients who received EBR/GZR were comparable with those who received placebo, with similar frequencies of AEs, serious AEs, and laboratory abnormalities. Although the overall frequency of AEs was high, there were no increases in frequency in the EBR/GZR versus placebo treatment group. The C-EDGE Treatment-Experienced trial included treatment arms with or without RBV, and it was found that the RBV-containing treatment regimens were less well tolerated than the non–RBV containing treatment regimens. Fatigue, nausea, vomiting, dyspepsia, rash, and pruritus were observed more frequently in patients treated with RBV. The safety of EBR/GZR relative to other available HCV therapies is inconclusive without a direct or indirect comparative evaluation.

## Other Considerations

It is worth noting that Health Canada indicated that EBR/GZR may be used as recommended in patients with mild hepatic impairment (Child-Pugh A). It is also indicated that EBR/GZR is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B and C) due to the expected significant increase in GZR plasma concentration.[10]

Also of note is that there is a difference in the duration of treatments between the FDA and Health Canada indications, where the FDA-recommended dosage regimens and durations in patients with genotype 1 for EBR/GZR was based on baseline NS5A polymorphisms, and prior treatment experience

with PR versus protease inhibitors,[11] while the Health Canada recommendation was not based on NS5A polymorphisms but mainly driven by prior treatment experience; in addition, there was no differentiation between patients who were PR treatment–experienced and patients who were PR plus protease inhibitor treatment–experienced.[10] Conversely, the Health Canada reviewer report indicated that in patients with genotype 1, baseline NS3 RAVs were not associated with SVR12 but more than five-fold NS5A RAVs to EBR obviously impacted the SVR12 and the trend was more likely with a high viral load of the virus combined.[12]

## Conclusions

Based on data from eight trials (two randomized, double-blind, placebo-controlled trials that also compared EBR/GZR versus a historical control; two trials that compared EBR/GZR versus a historical control; and four uncontrolled, open-label trials), EBR/GZR was associated with high rates of SVR12 in patients with genotype 1 or 4 CHC infection, in both treatment-naive and treatment-experienced patients; in addition, a high SVR12 rate was reported in treatment-naive patients with genotype 1 or 4 CHC infection who were coinfected with HIV. In addition, EBR/GZR was associated with high rates of SVR12 in treatment-naive and treatment-experienced patients with genotype 1 CHC infection who have CKD. These SVR12 rates were higher than SVR12 rates reported for the historical comparator simeprevir plus PR, sofosbuvir plus RBV, and PR. In addition, when combined with sofosbuvir, EBR/GZR was associated with high rates of SVR12 in treatment-naive patients with genotype 3. The data were limited for some populations, specifically patients with genotype 3 or 4 CHC. HRQoL measures showed clinically insignificant changes from baseline, and differences between treatment groups and with treatment groups in each trial were inconsistent between the different HRQoL measures. Serious AEs and withdrawals due to AEs were very limited, indicating good tolerability of the evaluated medication. Characteristic AEs associated with pegylated interferon appeared to occur less frequently among patients treated with EBR/GZR. However, the relative efficacy and safety of EBR/GZR compared with more recent interferon-free HCV therapies is uncertain because of the absence of direct or indirect comparative evaluations.

**TABLE 1: SUMMARY OF RESULTS**

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER (Patients Had to Have CKD) | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** | **EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14)** | **EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12)** |
| **SVR12 (full analysis set)** | | | | | | | | | | |
| N (%) [95% CI] | 299 (94.6) [91.5 to 96.8] | NR | 207 (95.0) [91.2 to 97.5][a] | 115/122 (94.3) [88.5 to 97.7] | | NR | 97 (92.4) [85.5 to 96.7] | 103 (97.2) [92.0 to 99.4] | 14 (100.0) [76.8 to 100] | 10 (83.3) [51.6 to 97.9] |
| Difference (95% CI) | NR | | NA | NR | | | NR | | NA | NA |
| **Relapse (full analysis set)** | | | | | | | | | | |
| GT 1a | 9/157 (5.7) | NR | 5/144 (3.5) | 0 | | NR | 5 (8.2) | 0 | NA | NA |
| GT 1b | 1/131 (0.8) | NR | 1/44 (2.3) | 1/55 (1.8)[b] | | | 0 | 0 | NA | NA |
| GT 3 | NA | NA | NA | NA | | NA | NA | NA | 0 | 1 (8.3) |
| GT 4 | 0 | NR | 1/28 (3.6) | NA | NA | NA | 1 (11.1) | 0 | NA | NA |
| **SF-36 PCS, mean (SD) change from baseline** | | | | | | | | | | |
| Baseline | 51.69 (8.44) | 50.64 (8.57) | 50.93 (8.61) | NA | 42.49 (8.61) | 44.30 (8.20) | 50.85 (7.95) | 50.55 (8.14) | NA | NA |
| Mean (95% CI) change from baseline at week 12 | –0.11 (–0.83 to 0.62) | 0.50 (–0.60 to 1.61) | 0.89 (–0.07 to 1.86) | NA | 1.18 (–0.18 to 2.55) | –0.52 (–2.29 to 1.25) | 0.52 (–0.82 to 1.86) | **–2.35 (–3.96 to –0.75)** | NA | NA |
| Treatment difference mean (95% CI) | –0.61 (–2.01 to 0.79) | | NA | NA | 1.71 (–0.51 to 3.93) | | NR | | NA | NA |
| **SF-36 MCS, mean (SD) change from baseline** | | | | | | | | | | |
| Baseline | 47.90 (10.79) | 50.41 (9.20) | 46.88 (11.73) | NA | 48.44 (10.26) | 48.57 (8.96) | 49.97 (10.0) | 50.83 (9.19) | NA | NA |
| Mean (95% CI) change from baseline at week 12 | **1.28 (0.25 to 2.32)** | –1.04 (–2.79 to 0.70) | **1.46 (0.16 to 2.76)** | NA | –1.14 (–3.07 to 0.80) | –0.44 (–2.08 to 1.20) | 0.64 (–1.18 to 2.45) | **–3.67 (–5.44 to –1.89)** | NA | NA |
| Treatment difference mean (95% CI) | **2.33 (0.28 to 4.37**) | | NA | NA | –0.69 (–3.21 to 1.82) | | NR | | NA | NA |
| **SF-36 Vitality domain, mean (SD) change from baseline** | | | | | | | | | | |
| Baseline | 59.87 (22.61) | 60.94 (19.61) | 59.45 (22.28) | NA | 54.19 (21.50) | 57.22 (18.47) | 60.95 (20.36) | 62.80 (22.40) | NA | NA |
| Mean (95% CI) change from baseline at week 12 | **2.52 (0.18 to 4.87)** | 0.49 (–3.26 to 4.23) | **5.07 (2.48 to 7.67)** | NA | 0.07 (–3.80 to 3.93) | –2.96 (–6.66 to 0.74) | **4.42 (0.39 to 8.45)** | **–8.40 (–12.62 to –4.18)** | NA | NA |
| Treatment difference mean (95% CI) | 2.04 (–2.54 to 6.62) | | NA | NA | 3.03 (–2.29 to 8.35) | | NR | | NA | NA |

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER (Patients Had to Have CKD) | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** | **EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14)** | **EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12)** |
| **EQ-5D Visual Analogue Scale, mean (SD) change from baseline** | | | | | | | | | | |
| Baseline | 78.65 (17.66) | 80.06 (14.12) | 76.13 (18.00) | NA | NA | NA | 77.77 (17.51) | 77.39 (16.46) | NA | NA |
| Mean (95% CI) change from baseline at week 12 | **1.92 (0.30 to 3.54)** | –0.53 (–2.83 to 1.77) | **3.74 (1.70, 5.78)** | NA | NA | NA | 2.79 (–0.17 to 5.74) | –1.72 (–5.27 to 1.84) | NA | NA |
| Treatment difference mean (95% CI) | 2.45 (–0.65 to 5.55) | | NA | NA | NA | NA | NR | | NA | NA |
| **FACIT-F, mean (SD) change from baseline** | | | | | | | | | | |
| Baseline | 40.80 (10.90) | 41.04 (10.06) | 38.82 (11.69) | NA | NA | NA | 40.44 (9.73) | 41.72 (9.58) | NA | NA |
| Mean (95% CI) change from baseline at week 12 | 0.41 (–0.62 to 1.45) | 0.22 (–1.54 to 1.98) | **2.31 (1.02 to 3.59)** | NA | NA | NA | 1.42 (–0.49 to 3.34) | **–4.07 (–5.99 to –2.15)** | NA | NA |
| Treatment difference mean (95% CI) | 0.19 (–1.86 to 2.24) | | NA | NA | NA | NA | NR | | NA | NA |
| **Overall CLDQ-HCV score, mean (SD) change from baseline** | | | | | | | | | | |
| Baseline | 5.22 (1.29) | 5.35 (1.10) | 5.00 (1.36) | NA | NA | NA | 5.46 (1.06) | 5.51 (1.11) | NA | NA |
| Mean (95% CI) change from baseline at week 12 | **0.30 (0.15 to 0.44)** | **0.28 (0.10 to 0.46)** | **0.63 (0.39 to 0.87)** | NA | NA | NA | 0.24 (–0.01 to 0.48) | –0.12 (–0.40 to 0.15) | NA | NA |
| Treatment difference mean (95% CI) | 0.02 (-0.23, 0.26) | | NA | NA | NA | NA | NR | | NA | NA |
| **AEs** | | | | | | | | | | |
| Any AE | 213 (67.4) | 72 (68.6) | 161 (73.9) | 9 (81.8) | 84 (75.7) | 95 (84.1) | 74 (70.5) | 95 (89.6) | 3 (21.4) | 4 (33.3) |
| SAE | 9 (2.8) | 3 (2.9) | 2 (0.9) | 0 | 16 (14.4) | 19 (16.8) | 4 (3.8) | 4 (3.8) | 0 | 1 (8.3) |
| Discontinuation due to AE | 3 (0.9) | 1 (1.0) | 0 | 0 | 0 | 5 (4.4) | 1 (1.0) | 5 (4.7) | 0 | 0 |

AE = adverse event; CI = confidence interval; CKD = chronic kidney disease; CLDQ-HCV = HCV-specific version of the Chronic Liver Disease Questionnaire; EBR = elbasvir; EQ-5D = EuroQoL 5-Dimensions Health-Related Quality of Life Questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; GT = genotype; GZR = grazoprevir; MCS = mental component summary; NA = not applicable; NR = not reported; PBO = placebo; PCS = physical component summary; PK = pharmacokinetic; RBV = ribavirin; SAE = serious adverse event; SD = standard deviation; SF-36 = Short Form 36-Item Health Survey; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; WPAI = Work Productivity and Activity Impairment questionnaire.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

[a] In the article by Rockstroh et al.,[34] it was reported that 210 (96.3%) of the 218 patients achieved SVR12, with a 95% CI of (92.9%, 98.4%), while the number of patients with genotype 1a who achieved SVR12 was 139 (96.5%) out of 144.

[b] The modified full analysis set population is a subset of the FAS population with patients excluded for the following reasons: failure to receive at least one dose of active study treatment, missing data due to death with reasons unrelated to study drug or reasons other than liver disease, and missing data due to study discontinuation with reasons unrelated to progression of liver disease, study drug and their responses to the HCV treatment.

**TABLE 1: SUMMARY OF RESULTS (CONT'D)**

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT1b: EBR/GZR for 12 Weeks (n = 13)** | **TN NC GT1a: EBR/GZR for 12 Weeks (n = 31)** | **TN NC GT1b: EBR/GZR for 8 Weeks (n = 31)** | **TN HIV NC GT1: EBR/GZR for 12 Weeks (n = 30)** | **TN C GT1: EBR/GZR for 12 Weeks (n = 29)** | **Null responder GT1: EBR/GZR for 12 Weeks (n = 33)** | **EBR/GZR + RBV for 12 Weeks (n = 79)** | **EBR/GZR for 12 Weeks (n = 19)** |
| **SVR12 (full analysis set)** | | | | | | | | |
| N (%)<br>[95% CI] | 13 (100.0)<br>[75.3 to 100.0] | 30 (96.8)<br>[83.3 to 99.9] | 29 (93.5)<br>[78.6 to 99.2] | 26 (86.7)<br>[69.3 to 96.2] | 28 (96.6)<br>[82.2 to 99.9] | 30 (90.9)<br>[75.7 to 98.1] | 76 (96.2)<br>[89.3 to 99.2] | 9/10 (90.0)<br>[55.5 to 99.7][a] |
| **Relapse (full analysis set) at follow-up week 12** | | | | | | | | |
| GT 1a, n/N (%) | NA | 1/30 (3.3) | NA | 0 | 1/20 (5.0) | 2/22 (9.1) | 2/30 (6.7) | 0 |
| GT 1b, n/N (%) | 0 | 0 | 2/31 (6.5) | 0 | 0 | 1/11 (9.1) | 1/49 (2.0) | 0 |
| **AEs** | | | | | | | | |
| Any AE | 11 (91.7) | 27 (87.1) | 17 (54.8) | 16 (53.3) | 19 (65.5) | 26 (78.8) | 63 (79.7) | 15 (78.9) |
| SAE | 0 | 0 | 0 | 1 (3.3) | 2 (6.9) | 1 (3.0) | 4 (5.1) | 0 |
| Discontinuation due to AE | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3) | 1 (5.3) |

AE = adverse event; C = cirrhotic; CI = confidence interval; EBR = elbasvir; GT = genotype; GZR = grazoprevir; HIV = human immunodeficiency virus; NC = non-cirrhotic; RBV = ribavirin; SAE = serious adverse event; SVR12 = sustained virologic response 12 weeks after the end of treatment; TN = treatment-naive.

Source: Clinical Study Reports: C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE.[20]

[a] Only genotype 4 patients included in this cell.

# 1. INTRODUCTION

## 1.1 Disease Prevalence and Incidence

Hepatitis C infection is caused by an enveloped, single-stranded linear ribonucleic acid (RNA) virus of the Flaviviridae family. In 2013, an estimated 250,000 Canadians had chronic hepatitis C (CHC) virus infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[1] A total of 11,357 cases of HCV were reported in Canada in 2009, mostly due to injection drug use.[2] Hepatitis C most commonly affects people older than 30 years, and disproportionately men, although the gender gap is narrowing.[2] Other populations at higher risk for HCV infection include federal inmates, men who have sex with men, street-involved youth, and Aboriginal peoples.[2] There are six major hepatitis C virus (HCV) genotypes, of which genotype 1 infections are the most common in Canada (65%).[1] Genotypes 2 and 3 are the next most common, estimated to make up 14% and 20% of HCV infections in Canada.[1] Genotype 4 is less common in Canada and accounts for less than 1% of HCV cases.[1]

Of those infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic infection.[21-23] Of those with chronic infection, 15% to 25% will develop progressive liver disease, end-stage liver disease, or hepatocellular carcinoma, or will require liver transplant.[3] Male gender, alcohol use, human immunodeficiency virus (HIV) coinfection, obesity, and increasing age are associated with an increased risk of liver disease progression.[3,24] While the incidence of HCV infection appears to be stable or declining in North America and Canada, it is expected that liver-related morbidity and mortality will continue to increase over the coming decades, as those who are already infected age.[1,4-7]

## 1.2 Standards of Therapy

The treatment paradigm for CHC infection continues to evolve rapidly. Prior to 2011, pegylated interferon (peginterferon) plus ribavirin (PR) was the gold standard therapy for patients with CHC infection. Approximately half of patients infected with genotype 1 HCV could expect to achieve sustained virologic response (SVR) with a 48-week course of PR therapy.[8] In recent years, greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral agents (DAAs) that target several types of nonstructural proteins used to support viral replication (Table 3). These regimens resulted in a further advance in SVR rates as compared with PR regimens that did not include a DAA. The first DAAs approved in Canada (boceprevir, telaprevir, simeprevir, and sofosbuvir) were used in combination with PR in patients with genotype 1 CHC (Table 4). A major limitation to PR-based treatment regimens has been their low tolerability. A number of interferon-free DAA regimens have now been approved in Canada for genotypes 1, 2, 3, and 4 CHC, with improved tolerability, high response rates, and shorter treatment durations (Table 5).[8] The treatment paradigm for hepatitis C has been shifting rapidly as new evidence emerges. Use of the protease inhibitors (PIs) boceprevir and telaprevir has been replaced by newer DAA regimens; telaprevir is no longer marketed in Canada, and boceprevir will soon be discontinued as well.[8] The recommendation from the CADTH Canadian Drug Expert Committee on the CADTH therapeutic review of drugs for CHC infection was that ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir + dasabuvir with or without ribavirin were preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status; daclatasvir/sofosbuvir for 12 weeks for patients with CHC genotype 3 infection, without cirrhosis; sofosbuvir/ribavirin for 24 weeks for patients with CHC genotype 3 infection, with cirrhosis; and SOF + PR for 12 weeks in treatment-naive, non-cirrhotic patients with CHC genotype 4 infection.[25]

## 1.3 Drug

Zepatier is a combination of elbasvir (EBR) and grazoprevir (GZR). EBR/GZR is formulated in one tablet; the tablet is composed of 50 mg EBR and 100 mg GZR. The recommended dosage is one tablet daily of Zepatier alone or in combination with other drugs for genotypes 1, 3, and 4 CHC (Table 2).

| **Indication under review** |
|---|
| Alone or in combination with other agents for the treatment of chronic hepatitis C (CHC) genotypes 1, 3, or 4 infections in adults |
| **Reimbursement criteria requested by sponsor** |
| As per indication |

**TABLE 2: ELBASVIR/GRAZOPREVIR DOSING BY HEPATITIS C VIRUS GENOTYPE**

| Population | Regimen | Duration |
|---|---|---|
| Genotype 1 TN,[a] PR-TE[b] relapsers, or PI/PR-TE[c] relapsers<br>or<br>Genotype 1b PR-TE or PI/PR-TE on-treatment virologic failures[d] | EBR/GZR (50 mg/100 mg) once daily | 12 weeks<br><br>(8 weeks may be considered in treatment-naive genotype 1b[e] patients without significant fibrosis or cirrhosis[f]) |
| Genotype 1a PR-TE or PI/PR-TE on-treatment virologic failures[d] | EBR/GZR (50 mg/100 mg) once daily + ribavarin[g,h] | 16 weeks |
| Genotype 3 TN | EBR/GZR (50 mg/100 mg) + SOF 400 mg daily | 12 weeks |
| Genotype 4 TN[a] or PR-TE[b] relapsers | EBR/GZR (50 mg/100 mg) once daily | 12 weeks |
| Genotype 4 PR-TE on-treatment virologic failures[d] | EBR/GZR (50 mg/100 mg) once daily + ribavirin[gh] | 16 weeks |

PI = protease inhibitor; PR = pegylated interferon plus ribavirin; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive.

[a] TN: Treatment-naive.

[b] PR-TE: Patients who failed treatment with pegylated interferon alfa + ribavirin.

[c] PI/PR-TE: Patients who failed pegylated interferon alfa + ribavirin + boceprevir, simeprevir, or telaprevir.

[d] On-treatment virologic failures are patients who have had a null response, partial response, virologic breakthrough or rebound, or intolerance to prior treatment.

[e] Includes patients with known genotype 1 subtypes other than 1a or 1b.

[f] Patients without clinically significant fibrosis or cirrhosis as determined by liver biopsy (i.e., METAVIR F0 to F2) or by non-invasive tests.

[g] In clinical trials, the dose of ribavirin was weight-based (< 66 kg = 800 mg/day; 66 to 80 kg = 1,000 mg/day; 81 to 105 kg = 1,200 mg/day; > 105 kg = 1,400 mg/day) administered in 2 divided doses with food.

[h] Patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 $m^2$) or with end-stage renal disease should receive Zepatier 12 weeks without ribavirin.

Source: Zepatier Draft Product Monograph.[10]

**TABLE 3: KEY CHARACTERISTICS OF DIRECT-ACTING ANTIVIRAL AGENTS APPROVED FOR USE IN CANADA**

| Drug | Mechanism of Action | Health Canada Indication | Serious Side Effects/Safety Issues |
|---|---|---|---|
| Simeprevir | HCV NS3/4A protease inhibitor: the protease is essential for viral replication. | Treatment of CHC genotype 1 or genotype 4 infection, in combination with PR in adults with compensated liver disease, including cirrhosis.<br><br>*Conditional marketing authorization:* Treatment of genotype 1 CHC use in combination with sofosbuvir in adults with compensated liver disease. | Rash, pruritus, nausea |
| Sofosbuvir | HCV NS5B polymerase inhibitor. The NS5B polymerase is an RNA polymerase that is critical for the viral replication cycle. | Treatment of genotype 1 CHC infection in adults in combination with ledipasvir.<br><br>Treatment of genotypes 1 and 4 CHC infection in combination with PR.<br><br>Treatment of genotypes 2 and 3 CHC infection in combination with ribavirin. | Fatigue, headache, insomnia |
| Ledipasvir | HCV NS5A inhibitor. The NS5A protein is an essential component of HCV replicase even though no known enzymatic function has been associated with it. | Treatment of genotype 1 CHC infection in adults in combination with sofosbuvir. | Fatigue, headache |
| Ombitasvir/ paritaprevir/ ritonavir and dasabuvir ± ribavirin | Ombitasvir: HCV NS5A inhibitor, which inhibits viral replication.<br><br>Paritaprevir: HCV NS3/4A protease inhibitor, which inhibits viral replication.<br><br>Dasabuvir: Non-nucleoside polymerase inhibitor encoded by the NS5B gene, which is essential for replication of the viral genome.<br><br>Ritonavir: Pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir. It is not active against HCV. | Treatment of adults with genotype 1 CHC infection including those with compensated cirrhosis. | Fatigue, headache, nausea, pruritus, and insomnia |

| Drug | Mechanism of Action | Health Canada Indication | Serious Side Effects/Safety Issues |
|---|---|---|---|
| Ombitasvir/ paritaprevir/ ritonavir ± ribavirin | Ombitasvir: HCV NS5A inhibitor, which inhibits viral replication.<br><br>Paritaprevir: HCV NS3/4A protease inhibitor, which inhibits viral replication.<br><br>Ritonavir: pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir. It is not active against HCV. | Treatment of CHC genotype 4 infection in adults without cirrhosis. | Fatigue, headache, nausea, pruritus, and insomnia |
| Daclatasvir | Inhibitor of the NS5A replication complex. | In combination with sofosbuvir for the treatment of CHC in adult patients with HCV genotypes 1 or 2 infection and compensated liver disease, including cirrhosis.<br><br>*Conditional marketing authorization:*<br>In combination with other drugs for the treatment of CHC in adult patients with HCV genotype 3 infection and compensated liver disease, including cirrhosis. | Headache and fatigue |
| Elbasvir/ grazoprevir | Elbasvir is an HCV NS5A inhibitor.<br>Grazoprevir is an HCV NS3/4A protease inhibitor. | Alone or in combination with ribavirin for the treatment of CHC genotypes 1, or 4 infection in adults.<br><br>In combination with sofosbuvir for the treatment of CHC genotype 3 infection in treatment-naive adult patients. | Nausea, headache, and fatigue |

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; NS5B = nonstructural protein B; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; RNA = ribonucleic acid.
Source: Product monographs.[10,26-32]

**TABLE 4: DOSING REGIMENS FOR DIRECT-ACTING ANTIVIRAL AGENTS USED IN COMBINATION WITH PEGYLATED INTERFERON AND RIBAVIRIN**

| HCV | Simeprevir | Sofosbuvir |
|---|---|---|
| **Genotype 1** | Simeprevir 150 mg capsule once daily with PR<br><br>**Treatment-naive:** triple therapy for 12 weeks, followed by PR for additional 12 or 36 weeks based on RGT<br><br>**Treatment-experienced:** triple therapy for 12 weeks, plus PR for additional 12 or 36 weeks based on RGT (prior-relapsers), or for an additional 36 weeks (prior partial and null responders)<br><br>**Cirrhotic patients**: As per above; no special dosing | Sofosbuvir 400 mg tablet, once daily with PR for 12 weeks |
| **Genotype 4** | Similar to genotype 1 dosing | 400 mg tablet, once daily with PR for 12 weeks |

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy.
Source: Product monographs.[26,30,31]

**TABLE 5: RECOMMENDED DOSING FOR INTERFERON-FREE DIRECT-ACTING ANTIVIRAL AGENT REGIMENS**

| HCV | Simeprevir/ Sofosbuvir | Sofosbuvir/Ribavirin | Sofosbuvir/ Ledipasvir | Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir | Ombitasvir/Paritaprevir/ Ritonavir | Daclatasvir/Sofosbuvir | Elbasvir/ Grazoprevir |
|---|---|---|---|---|---|---|---|
| **Genotype 1** | Simeprevir 150 mg capsule once daily with sofosbuvir 400 mg tablet, once daily for 12 weeks<br><br>TN, prior relapse patients and prior non-responder patients (including partial and null responders) with or without cirrhosis, who are not coinfected with HIV. | Sofosbuvir 400 mg once daily in combination with ribavirin for 24 weeks can be considered as a therapeutic option for TN and non-cirrhotic TE CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen. | Sofosbuvir 400 mg fixed dose combination tablet with 90 mg ledipasvir once daily for 12 weeks (24 weeks for TE patients with cirrhosis; 8 weeks can be considered for TN patients with HCV RNA > 6 million IU/mL). | Two fixed dose ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening).<br><br>**Genotype 1b, without cirrhosis**<br>12-week treatment duration<br><br>**Genotype 1a, without cirrhosis**<br>12-week treatment duration, combined with ribavirin<br><br>**Genotype 1a and 1b, with cirrhosis**<br>12-week treatment duration, combined with ribavirin (24-week treatment duration recommended for genotype 1a infection with cirrhosis who have had a previous null response to PR). | | Daclatasvir 60 mg tablet daily plus sofosbuvir 400 mg tablet daily (TN, or TE)[a]<br><br>**Without cirrhosis**<br>12 weeks<br><br>**With cirrhosis**<br>24 weeks | One fixed dose elbasvir 50 mg/grazoprevir 100 mg tablet once daily<br><br>**TN, PR-TE relapsers, or PI/PR-TE relapsers**<br>12 weeks<br>(8 weeks may be considered in treatment-naive genotype 1b patients without significant fibrosis or cirrhosis)<br><br>**PR-TE or PI/PR-TE on-treatment virologic failures**<br>12 weeks for genotype 1b (PR-TE or PI/PR-TE)<br><br>Combined with ribavirin for 16 weeks for genotype 1a (PR-TE or PI/PR-TE) |
| **Genotype 3** | | Sofosbuvir 400 mg tablet once daily in combination with ribavirin for 24 weeks. | | | | Daclatasvir 60 mg tablet daily plus sofosbuvir 400 mg tablet daily (TN, or TE)[a]<br><br>**Without cirrhosis**<br>12 weeks<br><br>**With cirrhosis**<br>24 weeks (ribavirin may be added in patients with cirrhosis) | One fixed dose elbasvir 50 mg/grazoprevir 100 mg tablet once daily<br><br>**TN**<br>In combination with sofosbuvir 400 mg for 12 weeks |

| HCV | Simeprevir/ Sofosbuvir | Sofosbuvir/Ribavirin | Sofosbuvir/ Ledipasvir | Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir | Ombitasvir/Paritaprevir/ Ritonavir | Daclatasvir/Sofosbuvir | Elbasvir/ Grazoprevir |
|---|---|---|---|---|---|---|---|
| **Genotype 4** | | | | | **TN or PR-TE without cirrhosis**<br>Two fixed dose ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg tablets taken once daily (in the morning) for 12 weeks combined with ribavirin. Ombitasvir/paritaprevir/ritonavir administered without ribavirin for 12 weeks may be considered for TN patients who cannot take or tolerate ribavirin. | | One fixed dose elbasvir 50 mg/grazoprevir 100 mg tablet once daily<br>**TN or PR-TE relapsers**<br>12 weeks<br>**PR-TE**<br>Combined with ribavirin for 16 weeks |

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; RNA = ribonucleic acid; TE = treatment-experienced; TN = treatment-naive.

[a] Daclatasvir dose should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4. Co-administration with strong or moderate CYP3A4 inhibitors is contraindicated with regimens that include asunaprevir. The dose of daclatasvir should be increased to 90 mg once daily (three 30 mg tablets or one 60 mg and one 30 mg tablet) when co-administered with moderate inducers of CYP3A4.

Source: Product monographs.[10,27-32]

# 2. OBJECTIVES AND METHODS

## 2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of EBR/GZR for the treatment of CHC genotypes 1, 3, and 4.

## 2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 6.

**TABLE 6: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW**

| | |
|---|---|
| **Patient Population** | Adults with CHC genotypes 1, 3, and 4 infection<br>Subpopulations:<br>• Treatment history (treatment-naive, or prior relapse, partial response, null response, intolerant to, or ineligible to receive PR or DAA therapy)<br>• Fibrosis level<br>• Cirrhosis<br>• HIV coinfection<br>• Hepatitis B coinfection<br>• Genotype subtype 1a or 1b<br>• Renal insufficiency<br>• Liver transplant<br>• Decompensated liver disease<br>• HCV RNA levels |
| **Intervention** | EBR/GZR 50/100 mg once daily alone for 12 weeks for patients with CHC genotypes 1, or 4 who are treatment-naive or treatment-experienced relapsers, or patients with CHC genotype 1b who are treatment-experienced on-treatment virologic failures.[a]<br><br>EBR/GZR 50/100 mg once daily in combination with ribavirin for 16 weeks for patients with CHC genotypes 1a or 4 who are treatment-experienced on-treatment virologic failures.[a]<br><br>EBR/GZR 50/100 mg once daily in combination with sofosbuvir for 12 weeks for patients with CHC genotype 3 who are treatment-naive. |
| **Comparators** | **Genotype 1**<br>• Ledipasvir/sofosbuvir<br>• Ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin<br>• Daclatasvir in combination with sofosbuvir<br>• Simeprevir in combination with PR<br>• Sofosbuvir in combination with PR<br>• Sofosbuvir in combination with ribavirin<br>• Simeprevir plus sofosbuvir<br>• Placebo in combination with PR<br>• Placebo or no treatment<br><br>**Genotype 3**<br>• Sofosbuvir in combination with ribavirin<br>• Daclatasvir in combination with sofosbuvir<br>• Sofosbuvir in combination with PR<br>• Placebo in combination with PR<br>• Placebo or no treatment |

| | |
|---|---|
| | **Genotype 4**<br>• Ombitasvir/paritaprevir/ritonavir (non-cirrhotic patients)<br>• Sofosbuvir in combination with PR<br>• Simeprevir in combination with PR<br>• Placebo in combination with PR<br>• Placebo or no treatment |
| **Outcomes** | **Key efficacy outcomes**<br>• Sustained virologic response[b]<br>• Virologic failure<br>• Relapse<br>• HRQoL[b]<br>• Other patient-reported outcomes (e.g., symptom scales, measure of mental health, psychological and/or emotional distress)[b]<br>• Mortality (all cause and liver-related)<br><br>**Other efficacy outcomes**<br>• Hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, liver transplant).<br>• SAE, WDAE, AE<br>• Harms of special interest (nausea, fatigue, anemia, pruritus, headache, ALT elevations) |
| **Study Design** | Published and unpublished phase 3 RCTs |

AE = adverse events; ALT = alanine aminotransferase; CHC = chronic hepatitis C; DAA = direct-acting antiviral agent; DB = double-blind; EBR = elbasvir; HCV = hepatitis C virus; HRQoL = health-related quality of life; PR=pegylated interferon plus ribavarin; RCT = randomized controlled trial; RNA = ribonucleic acid; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] On-treatment virologic failures are patients who have had a null response, partial response, virologic breakthrough or rebound, or intolerance to prior treatment.

[b] These outcomes were identified from the patient input.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were grazoprevir and elbasvir.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 26, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on April 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and

through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 7; excluded studies (with reasons) are presented in APPENDIX 3.

# 3. RESULTS

## 3.1 Findings From the Literature

A total of eight studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 7, and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

**FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES**

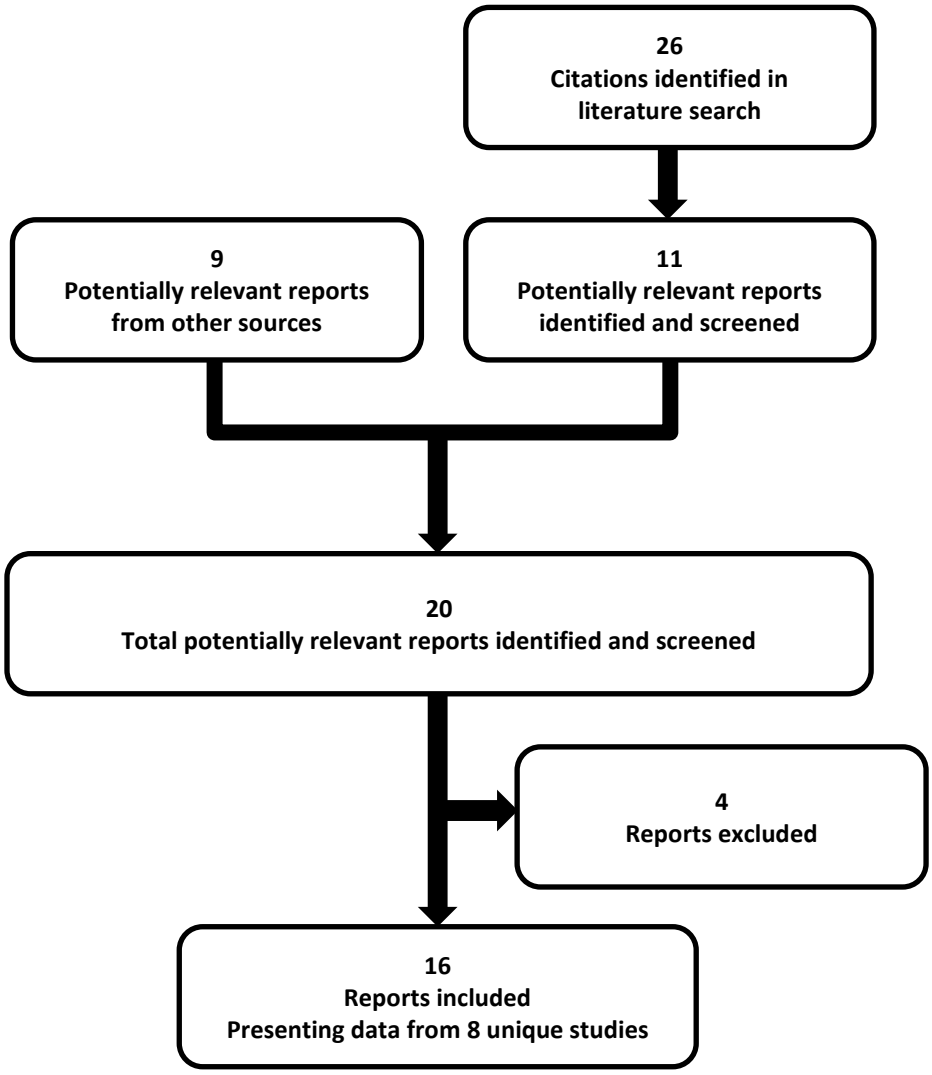


**TABLE 7: DETAILS OF INCLUDED STUDIES**

| | | Treatment-Naive Patients | | Mixed Experience | Treatment-Experienced Patients | Treatment-Naive Patients |
|---|---|---|---|---|---|---|
| | | **C-EDGE Treatment-Naive** | **C-EDGE Coinfection** | **C-SURFER** | **C-EDGE Treatment-Experienced** | **C-SWIFT** |
| DESIGNS & POPULATIONS | **Study Design** | DB, placebo-controlled RCT | OL, single group | DB, placebo-controlled RCT, and one addition non-randomized OL arm | Randomized, parallel-group, OL trial | Randomized (4 cohorts, with randomization taking place in 3 cohorts), parallel-group, single-centre, OL trial |
| | **Locations** | Asia, Australia, Europe, and US | Australia, Canada, Europe, Israel, and US | Argentina, Asia, Australia, Canada, Europe, and US | Asia, Australia, Canada, Europe, and US | US |
| | **Randomized (N)** | 421 | 218 | 237 | 420 | 143 |
| | **Inclusion Criteria** | • Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at the time of screening<br>• Treatment-naive with GT 1, 4, or 6 CHC | • Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at the time of screening<br>• Treatment-naive with GT 1, 4, or 6 CHC<br>• Coinfected with HIV | • Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at the time of screening<br>• Treatment-naive or treatment-experienced (prior IFN or PR treatment failures) with GT 1 CHC<br>• Have chronic kidney disease, defined as: patients with GFR ≤ 29 who are NDD or have been on HD for at least 3 months (including patients awaiting kidney transplant and patients with failed kidney transplants no longer on immunosuppressant therapy). | • Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at the time of screening<br>• Treatment-experienced with GT 1, 4, or 6 CHC | • Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at the time of screening<br>• Treatment-naive with GT 1 or 3 CHC |
| | **Exclusion Criteria** | • Coinfection with HIV or hepatitis B<br>• Decompensated liver disease<br>• HCC or is under evaluation for HCC<br>• Has a history of malignancy ≤ 5 years prior to signing informed consent<br>• Previous organ transplant<br>• Recent substance abuse<br>• CrCl < 50 mL/min | • Coinfection with hepatitis B<br>• Decompensated liver disease<br>• HCC or is under evaluation for HCC<br>• Has a history of malignancy ≤ 5 years prior to signing informed consent<br>• Previous organ transplant<br>• Recent substance abuse<br>• CrCl < 50 mL/min | • Coinfection with HIV or hepatitis B<br>• On peritoneal dialysis for management of kidney disease<br>• Decompensated liver disease<br>• HCC or is under evaluation for HCC<br>• Has a history of malignancy ≤ 5 years prior to signing informed consent<br>• Previous organ transplant other than kidney<br>• Recent substance abuse | • Coinfection with hepatitis B<br>• Decompensated liver disease<br>• HCC or is under evaluation for HCC<br>• Has a history of malignancy ≤ 5 years prior to signing informed consent<br>• Previous organ transplant<br>• Recent substance abuse<br>• CrCl < 50 mL/min | • Coinfection with HIV or hepatitis B<br>• Decompensated liver disease<br>• HCC or is under evaluation for HCC<br>• Has a history of malignancy ≤ 5 years prior to signing informed consent<br>• Previous organ transplant<br>• Recent substance abuse<br>• CrCl < 50 mL/min |

| | | Treatment-Naive Patients | | Mixed Experience | Treatment-Experienced Patients | Treatment-Naive Patients |
|---|---|---|---|---|---|---|
| | | **C-EDGE Treatment-Naive** | **C-EDGE Coinfection** | **C-SURFER** | **C-EDGE Treatment-Experienced** | **C-SWIFT** |
| DRUGS | **Intervention** | • 12 weeks of treatment with the fixed dose combination of EBR with GZR (50 mg EBR/100 mg GZR) | • 12 weeks of treatment with the fixed dose combination of EBR with GZR (50 mg EBR/100 mg GZR) | • 12 weeks of treatment with the fixed dose combination of EBR with GZR (50 mg EBR/100 mg GZR) | • EBR/GZR (50 mg EBR/100 mg GZR) for 12 weeks<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 12 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) for 16 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 16 weeks | **Treatment-Naive G1 Without Cirrhosis**<br>• 4 weeks of treatment with EBR/GZR (50 mg EBR/100 mg GZR), and 400 mg SOF[a]<br>or<br>• 6 weeks of treatment with EBR/GZR (50 mg EBR/100 mg GZR), and 400 mg SOF[a]<br>**Treatment-Naive G1 With Cirrhosis**<br>• 6 weeks of treatment with EBR/GZR (50 mg EBR/100 mg GZR), and 400 mg SOF[a]<br>or<br>• 8 weeks of treatment with EBR/GZR (50 mg EBR/100 mg GZR), and 400 mg SOF[a]<br>**Treatment-Naive G3 Without Cirrhosis**<br>• 8 weeks of treatment with EBR/GZR (50 mg EBR/100 mg GZR), and 400 mg SOF[a]<br>or<br>• 12 weeks of treatment with EBR/GZR (50 mg EBR/100 mg GZR), and 400 mg SOF<br>**Treatment-Naive G3 With Cirrhosis**<br>• 12 weeks of treatment with EBR/GZR (50 mg EBR/100 mg GZR), and 400 mg SOF |
| | **Comparator(s)** | • Placebo for the first 16 weeks then received the intervention<br>• Historical comparator (simeprevir plus PR) | • None<br>• Historical comparator (SOF plus RBV) | • Placebo for the first 16 weeks then received the intervention<br>• Reference SVR 12 rate | • None<br>• Historical comparator (simeprevir plus PR) | None |
| DURATION | **Phase** | 3 | 3 | 3 | 3 | **2** |
| | DB | 12 weeks | NA | 12 weeks | NA | NA |
| | OL | Patients in placebo group starting at week 16 will receive the intervention OL | 12 weeks | Patients in placebo group starting at week 16 will receive the intervention OL | 12 to 16 weeks | 4 to 12 weeks |
| | Follow-up | 24 weeks | 24 weeks | 24 weeks | 24 weeks | 24 weeks |

| | | Treatment-Naive Patients | | Mixed Experience | Treatment-Experienced Patients | Treatment-Naive Patients |
|---|---|---|---|---|---|---|
| | | **C-EDGE Treatment-Naive** | **C-EDGE Coinfection** | **C-SURFER** | **C-EDGE Treatment-Experienced** | **C-SWIFT** |
| OUTCOMES | **Primary End Point** | SVR12 versus historical comparator | | SVR12 versus reference SVR12 rate | SVR12 versus historical comparator | SVR12 |
| | | SVR12 for historical comparator = 73% | SVR12 for historical comparator = 70% | SVR12 for historical comparator = 45% | SVR12 for historical comparator = 58% | |
| | **Other End Points** | • SVR24<br>• SF-36v2<br>• EQ-5D-5L<br>• EQ VAS scores<br>• FACIT-Fatigue Scale score<br>• CLDQ-HCV scores<br>• WPAI<br>• Harms | • SVR24<br>• SF-36v2<br>• EQ-5D-5L<br>• EQ VAS scores<br>• FACIT-F score<br>• CLDQ-HCV scores<br>• WPAI<br>• Harms | SVR24<br>SF-36v2 | • SVR24<br>• SF-36v2<br>• EQ-5D-5L<br>• EQ VAS scores<br>• FACIT-Fatigue Scale score<br>• CLDQ-HCV scores<br>• WPAI<br>• Harms | SVR24 |
| NOTES | **Publications** | Zeuzem et al. 2015[33] | Rockstroh et al. 2015[34] | Roth et al. 2015[35] | None | None |

CHC = chronic hepatitis C; CLDQ-HCV = HCV-specific version of the Chronic Liver Disease Questionnaire; CrCl = creatinine clearance; DB = double-blind; DAA = direct-acting antiviral agent; EBR = elbasvir; EQ-5D = EuroQoL 5-Dimensions Health-Related Quality of Life Questionnaire; EQ VAS = EuroQol Visual Analogue Scale; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; GFR = glomerular filtration rate; GT = genotype; GZR = grazoprevir; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HD = hemodialysis; Hgb = hemoglobin; HIV = human immunodeficiency virus; IFN = interferon; NA = not applicable; NDD = non-dialysis dependent; OL = open-label; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RCT = randomized controlled trial; RNA = ribonucleic acid; SF-36 = Short Form 36-Item Health Survey; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; WPAI = Work Productivity and Activity Impairment questionnaire.

[a] Not Health Canada–recommended doses, hence not included in the review.

Note: One additional report was included.[36]

Source: Lawitz et al.;[37] Sulkowski et al.;[38] Buti et al.;[39] Forns et al.;[40] Roth et al.;[35] Zeuzem et al.;[33] Rockstroh et al.;[34] Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE;[20] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 7: DETAILS OF INCLUDED STUDIES (CONT'D)**

| | | C-WORTHY | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|
| DESIGNS & POPULATIONS | **Study Design** | Randomized (4-part trial with 7 cohorts, with randomization took place in all 4 parts), parallel-group, multi-centre, OL trial | OL, single group | Randomized (2 parts, with randomization taking place in 1 part), parallel-group, multi-centre, OL trial |
| | **Locations** | Australia, Canada, Europe, Israel, New Zealand, Puerto Rico, and US | Austria, Israel, Spain, and US | Australia, Europe, Israel, and US |
| | **Randomized (N)** | 573 | 79 | 98 |
| | **Inclusion Criteria** | **Part A:**<br>• Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at the time of screening<br>• Treatment-naive with GT 1a or GT 1b CHC | • Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at the time of screening | • Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at the time of screening<br>• Have documented chronic HCV GT2 (for part A) |

| | | C-WORTHY | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|
| | | • Have had a liver biopsy without evidence of advanced fibrosis, cirrhosis, and/or HCC<br><br>**Part B, Part C, and Part D:**<br>• Adults (aged ≥ 18 years)<br>• Have chronic, compensated HCV GT 1 (for Part B), GT 1b (for Part C), and GT 3 (for Part D)<br>• Have HCV RNA levels ≥ 10,000 IU/mL<br>• Treatment-naive in Part C and Part D<br>• Treatment-naive or treatment-experienced null responders to PR in Part B | • Have documented chronic HCV GT1<br>• Have received a prior regimen containing an approved DAA (boceprevir, telaprevir, simeprevir, or SOF) co-administered for at least 4 weeks with PR | • Have documented chronic HCV GT2, GT4, GT5, or GT6 (for part B)<br>• Had absence of cirrhosis |
| | **Exclusion Criteria** | **Part A:**<br>• Has a non-GT 1 HCV infection<br>• Is NOT treatment-naive<br>• Coinfection with HIV or hepatitis B<br>• Has evidence of HCC<br>• Has a clinical diagnosis of substance abuse within<br>• specified timeframes<br>• Has evidence of active or suspected malignancy, or a history of malignancy, within the last 5 years<br>• Prior organ transplant<br>• CrCl < 50 mL/min<br><br>**Part B, Part C, and Part D:**<br>• Has a non-GT 1 HCV infection (Part B, and Part C) or a non-GT3 HCV infection (Part D)<br>• Has previously received any HCV DAAs<br>• Evidence of decompensated liver disease<br>• Coinfection with HIV (except for study arms 12, 13, and 14 in Part B) or hepatitis B<br>• Has evidence of HCC or is under evaluation for HCC<br>• Has a clinical diagnosis of substance abuse within specified timeframes<br>• Has evidence of active or suspected malignancy, or a history of malignancy, within the last 5 years<br>• Previous organ transplant<br>• CrCl < 50 mL/min | • Has received any HCV regimen containing a DAA with the exception of boceprevir, telaprevir, simeprevir, or SOF in combination with PR.<br>• Has evidence of decompensated liver disease<br>• Coinfection with HIV or hepatitis B<br>• Has a history of malignancy ≤ 5 years prior to signing informed consent<br>• HCC or is under evaluation for HCC<br>• Has clinically relevant drug or alcohol abuse within 12 months of screening<br>• Previous organ transplant<br>• CrCl < 50 mL/min | • Had non-GT 2 HCV infection (for part A)<br>• Had HCV infection with a genotype other than GT 2, GT 4, GT 5, or G T6 (for part B)<br>• Is not treatment-naive (for part B)<br>• Coinfection with HIV or hepatitis B<br>• HCC or is under evaluation for HCC<br>• Had a clinical diagnosis of substance abuse within specified time frames<br>• Had evidence of active or suspected malignancy, or a history of malignancy, within the last 5 years<br>• Previous organ transplant<br>• CrCl < 50 mL/min |
| **DRUGS** | **Intervention** | **Part A** (treatment-naive and non-cirrhotic patients):<br>• For patients with HCV GT 1: EBR/GZR (20 mg EBR/100 mg GZR) + RBV for 12 weeks[a]<br>• For patients with HCV GT 1: EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 12 weeks[a]<br>• For patients with HCV GT 1 b: EBR/GZR (50 mg EBR/100 mg GZR) for 12 weeks | • GZR/EBR (100 mg GZR/50mg EBR) + RBV for 12 weeks[c] | **Part A** (patients with HCV GT2):<br>• GZR/EBR (100 mg GZR/50mg EBR) + RBV for 12 weeks[d] |

| | | C-WORTHY | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|
| | | **Part B:**<br>For treatment-naive non-cirrhotic patients:<br>• For patients with HCV GT 1a: EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 8 weeks[a]<br>• For patients with HCV GT 1: EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 12 weeks[a]<br>• For patients with HCV GT 1a: EBR/GZR (50 mg EBR/100 mg GZR) for 12 weeks<br><br>For treatment-naive cirrhotic patients with HCV GT 1:<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 12 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) for 12 weeks<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 18 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) for 18 weeks[a]<br><br>Null responders (cirrhotic and non-cirrhotic) with HCV GT 1:<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 12 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) for 12 weeks[b]<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 18 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) for 18 weeks[a]<br><br>Treatment-naive coinfected with HIV (non-cirrhotic) with HCV GT 1:<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 12 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) for 12 weeks<br><br>**Part C** (treatment-naive non-cirrhotic patients with HCV GT 1b):<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 8 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) for 8 weeks<br>**Part D** (treatment-naive non-cirrhotic patients with HCV GT 3):<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 12 weeks[a]<br>• EBR/GZR (50 mg EBR/100 mg GZR) + RBV for 18 weeks[a] | | **Part B:**<br>For patients with HCV GT2:<br>• GZR (100 mg GZR) + RBV for 12 weeks[d]<br><br>For patients with HCV GT4, GT5, or GT6:<br>• GZR/EBR (100 mg GZR/50mg EBR) + RBV for 12 weeks[a]<br>or<br>• GZR/EBR (100 mg GZR/50mg EBR) for 12 weeks |
| | **Comparator(s)** | None | None | None |
| **DURATION** | **Phase** | **2** | **2** | **2** |
| | DB | Only part A was DB for 2 of the arms that did not use the Health Canada–approved doses. Parts B, C, and D of the study were OL. | NA | NA |
| | OL | 8 to 18 weeks | 12 weeks | 12 weeks |
| | Follow-up | 24 weeks | 24 weeks | 24 weeks |
| **OU** | **Primary End Point** | SVR12 | SVR12 | SVR12 |

| | | C-WORTHY | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|
| | **Other End Points** | SVR24<br>Harms | SVR24<br>Harms | SVR24<br>Harms |
| NOTES | **Publications** | Sulkowski et al. 2015[38] | Forns et al. 2015[40] | None |

CHC = chronic hepatitis C; CLDQ-HCV = HCV-specific version of the Chronic Liver Disease Questionnaire; CrCl = creatinine clearance; DAA = direct-acting antiviral agent; DB = double-blind; EBR = elbasvir; EQ-5D = EuroQoL 5-Dimensions Health-Related Quality of Life Questionnaire; EQ VAS = EuroQol Visual Analogue Scale; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; GT = genotype; GZR = grazoprevir; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; Hgb = hemoglobin; HIV = human immunodeficiency virus; IFN = interferon; OL = open-label; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RCT = randomized controlled trial; SF-36 = Short Form 36-Item Health Survey; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; WPAI = Work Productivity and Activity Impairment questionnaire.

[a] Not Health Canada–recommended doses, hence not included in the review.

[b] This dose is approved only for patients with genotype 1b; hence, only those patients will be included in the review when possible.

[c] Not Health Canada–recommended doses; it was included in the review because this study was considered pivotal by the manufacturer.

[d] Not approved Health Canada indication; hence, not included in the review.

Note: One additional report was included.[36]

Source: Lawitz et al.;[37] Sulkowski et al.;[38] Buti et al.;[39] Forns et al.;[40] Roth et al.;[35] Zeuzem et al.;[33] Rockstroh et al.;[34] Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE;[20] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

## 3.2 Included Studies

### 3.2.1 Description of Studies

A total of eight trials were included in this review: three pivotal phase 3 clinical trials (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-EDGE Treatment-Experienced); three pivotal phase 2 clinical trials (C-SWIFT, C-WORTHY, C-SALVAGE); C-SURFER, which was a phase 3 clinical trial and was not pivotal but met our inclusion criteria; and C-SCAPE, which was a phase 2 trial that was considered pivotal by the manufacturer but not Health Canada (Table 7). The primary outcome in all trials was SVR12. All four phase 3 trials compared the active treatment arms to a historical comparator for the main outcome (SVR12).

C-EDGE Treatment-Naive was a phase 3, randomized, parallel-group, multi-site, double-blinded, placebo-controlled trial that evaluated the fixed dose combination (FDC) regimen of EBR/GZR among treatment-naive cirrhotic and non-cirrhotic patients with CHC genotype 1, 4, or 6 infection. Patients were randomized in a 3:1 ratio to an immediate treatment arm or a deferred treatment arm. Randomization was stratified by fibrosis stage (non-cirrhotic versus cirrhotic) and HCV genotype/subtype (genotype 1a versus genotype 1 non-a versus genotypes 4 or 6). Patients in the immediate treatment group received EBR 50 mg/GZR 100 mg for 12 weeks with planned 24 weeks of follow-up after dosing was completed. Patients in the deferred treatment group received placebo for 12 weeks followed by four weeks of follow-up and then 12 weeks of open-label treatment with EBR 50 mg/GZR 100 mg with planned 24 weeks of follow-up after dosing was completed.

C-EDGE Coinfection was a phase 3, open-label, multi-centre, single-arm study in treatment-naive cirrhotic and non-cirrhotic patients with CHC genotype 1, 4, or 6 infection, coinfected with HIV. All patients received a FDC regimen of EBR 50 mg/GZR 100 mg for 12 weeks with 24 weeks of follow-up once dosing had been completed.

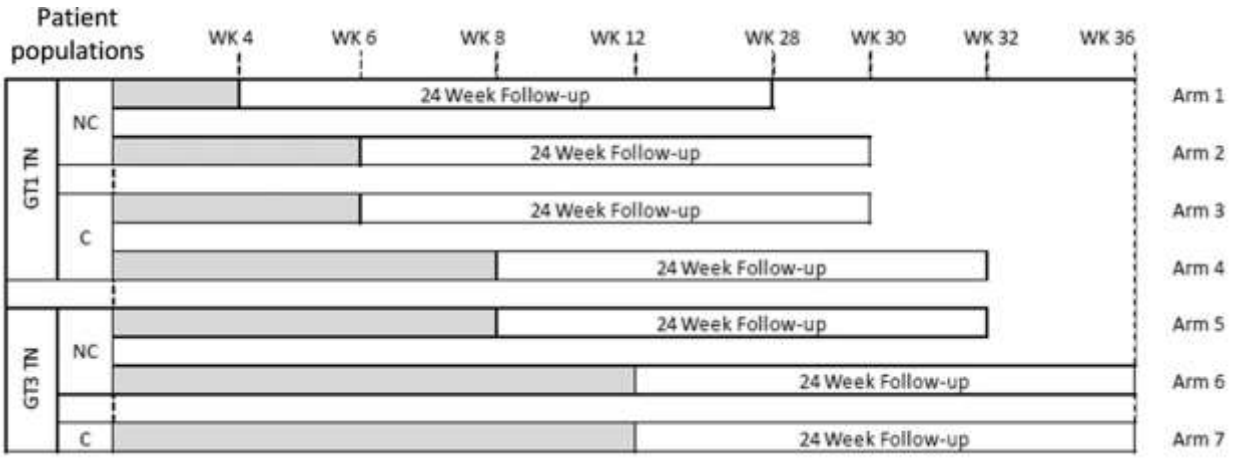
C-SURFER was a phase 3, randomized, parallel-group, multi-site, double-blind, placebo-controlled trial that enrolled cirrhotic and non-cirrhotic, CHC genotype 1 infection, who had chronic kidney disease (CKD), where CKD was defined as patients with glomerular filtration rate (GFR) ≤ 29 who are non-dialysis dependent or have been on hemodialysis for at least three months (including patients awaiting kidney transplant and patients with failed kidney transplants no longer on immunosuppressant therapy). Patients were randomized in a 1:1 ratio to an immediate treatment arm or a deferred treatment arm. Randomization was stratified by hemodialysis status at baseline and by presence of a diagnosis of diabetes mellitus at baseline. Patients in the immediate treatment group received an FDC EBR 50 mg/GZR 100 mg tablet once daily for 12 weeks with planned 24 weeks of follow-up after dosing was completed. Patients in the deferred treatment group received placebo for 12 weeks followed by four weeks of follow-up and then 12 weeks of open-label treatment with EBR 50 mg/GZR 100 mg with planned 24 weeks of follow-up after dosing was completed. The trial also included a small intensive pharmacokinetic (PK) arm: patients were to receive open-label EBR 50 mg/GZR 100 mg once daily for 12 weeks with 24 weeks of post dosing follow-up.

C-EDGE Treatment-Experienced was a phase 3, randomized, parallel-group, multi-site, open-label trial of EBR 50 mg/GZR 100 mg FDC tablets administered once daily with or without ribavirin (RBV) for 12 or 16 weeks to patients with HCV genotype 1, 4, or 6 infection, with and without compensated cirrhosis, who failed prior treatment with PR. Patients were randomized in a 1:1:1:1 ratio to receive 12 weeks of treatment with EBR 50 mg/GZR 100 mg once daily, 12 weeks of treatment with EBR 50 mg/GZR 100 mg once daily + RBV, 16 weeks of treatment with EBR 50 mg/GZR 100 mg once daily, or 16 weeks of treatment with EBR 50 mg/GZR 100 mg + RBV. Patients who received EBR 50 mg/GZR 100 mg + RBV for

12 weeks and patients who received EBR 50 mg/GZR 100 mg for 16 weeks did not meet this review's inclusion criteria, and these treatment arms have not been summarized in this report because the regimen used was different from the Health Canada–approved regimen.

C-SWIFT was a phase 2, randomized, parallel-group, open-label, single-centre, multiple-arm trial of EBR 50 mg/GZR 100 mg FDC and 400 mg sofosbuvir (SOF) in treatment-naive patients with chronic HCV genotype 1 (with compensated cirrhosis or without cirrhosis) or genotype 3 (with compensated cirrhosis or without cirrhosis) infection for four, six, eight, or 12 weeks. Within the genotype 1 non-cirrhotic, genotype 1 cirrhotic, and genotype 3 non-cirrhotic cohorts, a separate randomization assigned patients into one of four groups defined by duration of therapy (four weeks, six weeks, eight weeks, and 12 weeks) according to a computer-generated allocation schedule. Within each of the three cohorts, only two durations were used. Within the genotype 3 cirrhotic cohort, all patients were assigned to the 12-week duration group (no randomization). Randomization of patients within the genotype 1 cohorts (treatment arms 1 to 4) was stratified based on genotype subtype (1a versus non-1a). No stratification took place in the genotype 3 cohort (treatment arms 5 and 6). A schematic design of the C-SWIFT trial can be found in Figure 2. Patients with genotype 3 who received EBR 50 mg/GZR 100 mg + SOF 400 mg for eight weeks and patients with genotype 1 did not meet this review's inclusion criteria, and these treatment arms have not been summarized in this report because the regimen used was different from the Health Canada–approved regimen.

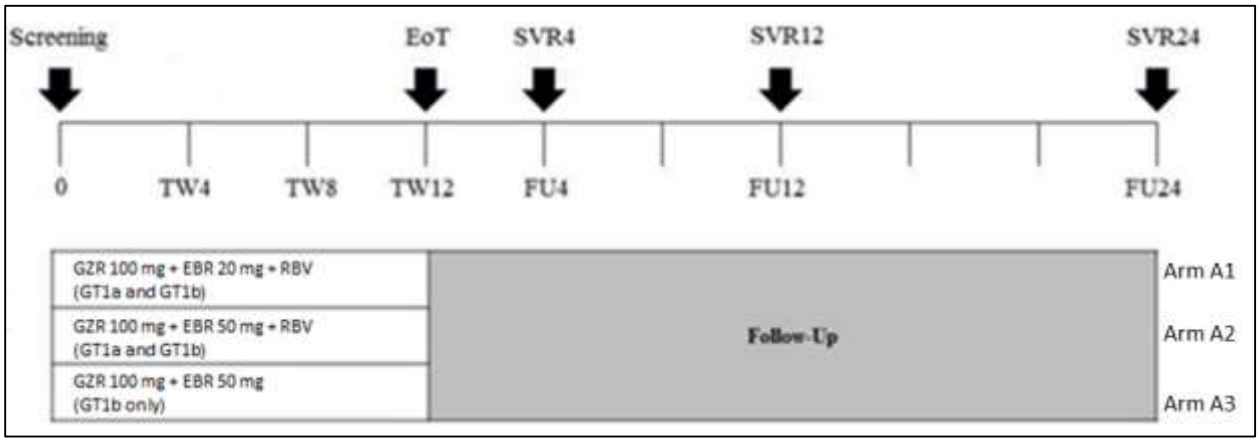
**FIGURE 2: TRIAL DESIGN OF C-SWIFT STUDY**




C = cirrhotic; GT = genotype; NC = non-cirrhotic; WK = week.
Source: Clinical Study Reports C-SWIFT.[14]

C-WORTHY was a phase 2, multi-centre, randomized, parallel-group trial that evaluated GZR 100 mg in combination with EBR 20 mg or 50 mg once daily with or without RBV for treatment of chronic hepatitis C. C-WORTHY included four parts. Part A was a double-blind, dose-response evaluation of 12-week regimens without active control in treatment-naive, non-cirrhotic patients infected with HCV genotype 1. In part A, patients were to be randomized in a 1:1 ratio to two treatment arms in which open-label GZR 100 mg once daily was administered concomitantly with double-blinded EBR doses of either 20 mg or 50 mg once daily, with twice-daily RBV. Patients in these two arms were stratified by HCV genotype (genotype 1a versus genotype 1b). A third arm of patients infected with genotype 1b received a regimen of GZR 100 mg and EBR 50 mg, without RBV. All arms were treated for 12 weeks and followed up for an additional 24 weeks after end of treatment. A schematic design for part A of the C-WORTHY trial can be found in Figure 3.

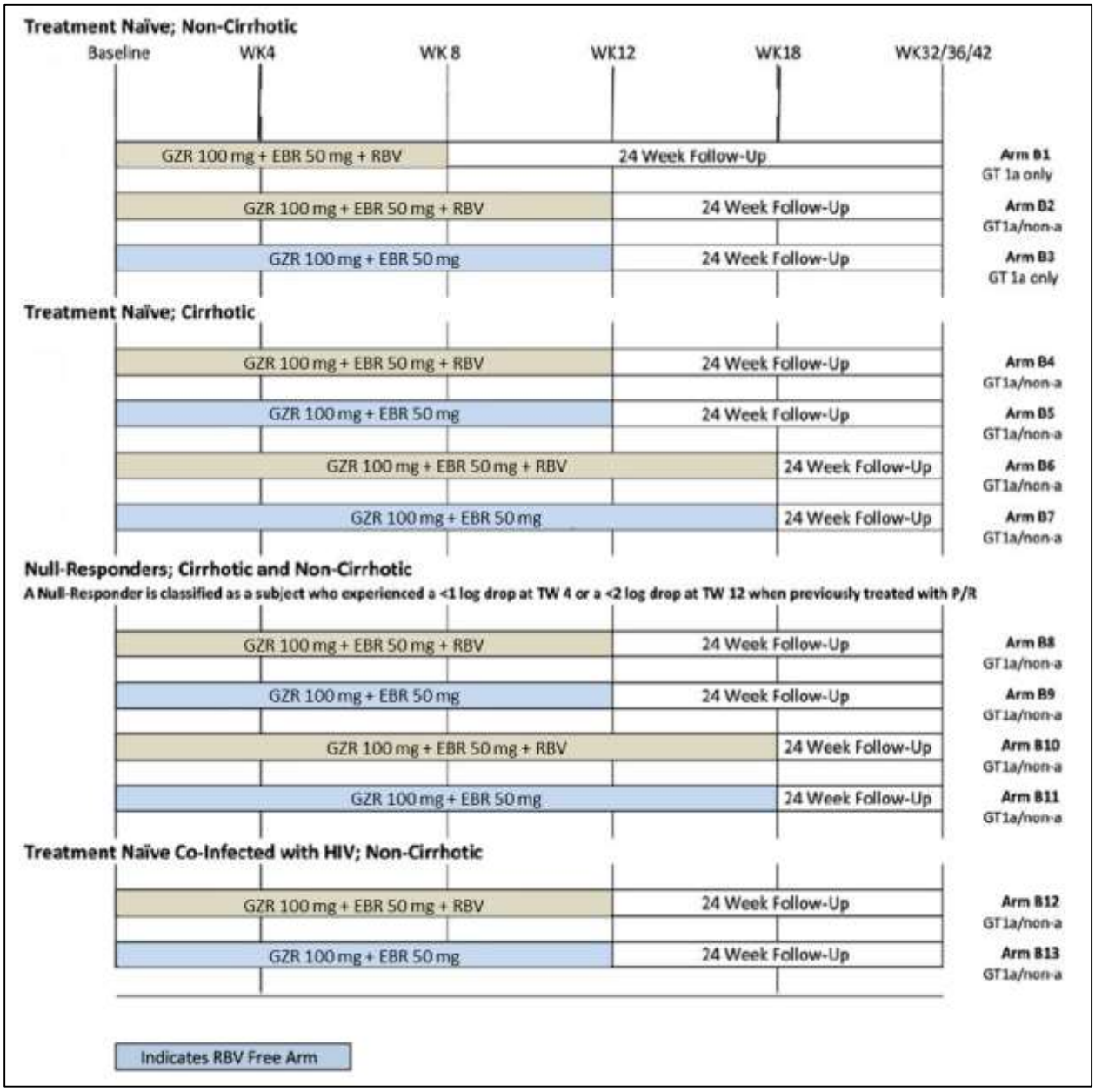
**FIGURE 3: TRIAL DESIGN FOR PART A OF C-WORTHY STUDY**




EBR = elbasvir; EoT = end of treatment; FU = follow-up; GT = genotype; GZR = grazoprevir; RBV = ribavirin; TW = treatment week; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment.
Source: Clinical Study Reports: C-WORTHY.[18]

Part B of the C-WORTHY trial evaluated eight, 12, and 18 weeks of open-label treatment without active control in patients with or without cirrhosis, prior null response, or HIV coinfection in which patients and sites were blinded to duration. Part B was open-label with respect to the dose of therapy administered, but the investigators and patients were blinded to the assignment treatment duration through week 8 or week 12. All arms were followed up for an additional 24 weeks after end of treatment. In treatment-naive non-cirrhotic patients (Arms B1 to B3), patients with HCV genotype 1a were randomized to three treatment arms in a ratio of 2:1:2 (Arms B1, B2, and B3). Patients with HCV genotype 1 (non-a) were all allocated to Arm B2. In treatment-naive cirrhotic patients (Arms B4 to B7), patients were randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of treatment with or without RBV. In null responder cirrhotic and non-cirrhotic patients (Arms B8 to B11), patients were randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of treatment with or without RBV. Treatment-naive non-cirrhotic patients coinfected with HIV (Arms B12 to B13) were randomized in a ratio of 1:1 to receive 12 weeks of treatment with or without RBV. Patients in treatment arms that included both HCV genotype 1a and 1b were distributed such that at least 40% of patients enrolled in each arm were genotype 1a. Additionally, in the patient population of prior null responders, enrolment was stratified by the presence or absence of cirrhosis. A schematic design for part B of the C-WORTHY trial can be found in Figure 4.

**FIGURE 4: TRIAL DESIGN FOR PART B OF C-WORTHY STUDY**




EBR = elbasvir; GT = genotype; GZR = grazoprevir; HIV = human immunodeficiency virus; P/R = pegylated interferon plus ribavirin; RBV = ribavirin; TW = treatment week; WK = week.
Source: Clinical Study Reports: C-WORTHY.[18]

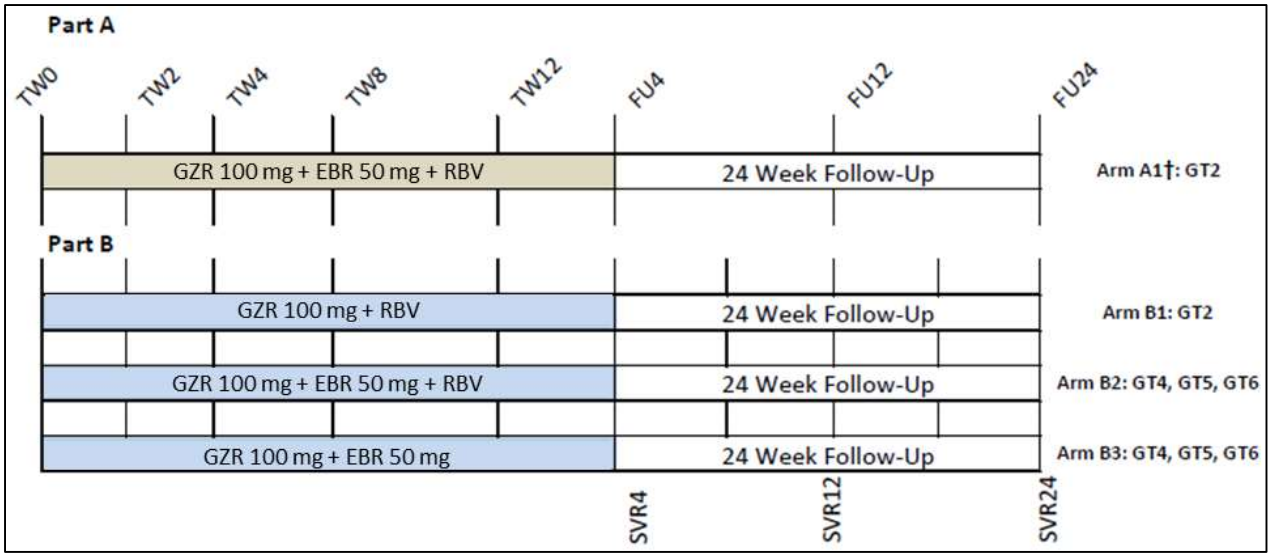
Part C of the C-WORTHY trial evaluated eight weeks of open-label treatment in treatment-naive, non-cirrhotic patients with HCV genotype 1b monoinfection. Patients were randomized to two treatment arms in a ratio of 1:1 to receive eight weeks of treatment with or without RBV. Part D evaluated 12 and 18 weeks of open-label treatment with EBR + GZR + RBV in treatment-naive non-cirrhotic patients infected with HCV genotype 3. From Part A, only the treatment arm that included treatment-naive and non-cirrhotic patients with HCV genotype 1b who were treated with EBR 50 mg/GZR 100 mg for 12 weeks was included. In part B, only the following treatment arms were

included: 1) treatment-naive non-cirrhotic patients with HCV genotype 1a treated with EBR 50 mg/GZR 100 mg for 12 weeks, 2) treatment-naive cirrhotic patients with HCV genotype 1 treated with EBR 50 mg/GZR 100 mg for 12 weeks, 3) prior null responders (cirrhotic and non-cirrhotic) patients with HCV genotype 1 treated with EBR 50 mg/GZR 100 mg for 12 weeks (this dose is approved only for patients with genotype 1b; hence, only those patients will be included in the review when possible), 4) treatment-naive patients coinfected with HIV (non-cirrhotic) with HCV genotype 1 treated with EBR 50 mg/GZR 100 mg for 12 weeks. From part C, only the treatment arm that included treatment-naive and non-cirrhotic patients with HCV genotype 1b who were treated with EBR 50 mg/GZR 100 mg for eight weeks was included. No treatment arm from part D was included in the review. Treatment arms were excluded from this review because the regimen used was different from the Health Canada–approved regimen.

C-SALVAGE was a phase 2, multi-site, open-label, single-arm study of EBR 50 mg/GZR 100 mg + RBV for 12 weeks in patients with chronic HCV genotype 1 infection who failed a prior approved DAA regimen of boceprevir, telaprevir, simeprevir, or sofosbuvir taken concomitantly with PR. The regimen used in this trial is not a Health Canada–recommended dose for this patient population, but this trial was included in the review because it was considered pivotal by the manufacturer.

C-SCAPE was a phase 2, multi-site, open-label, parallel-group trial evaluating the safety and efficacy of GZR 100 mg in combination with or without EBR 50 mg, and/or RBV in treating non-cirrhotic, treatment-naive patients with CHC infection with genotypes 2, 4, 5 and 6. C-SCAPE included two parts. Part A included only one treatment arm. Patients with genotype 2 infection were assigned to Arm A1 and were treated with EBR 50 mg/GZR 100 mg with ribavirin for 12 weeks. There were three treatment arms in part B. Patients with genotype 2 infection were assigned to Arm B1 (GZR 100 mg + RBV for 12 weeks). Patients with genotype 4, 5, or 6 infection were randomized in a 1:1 ratio to either Arm B2 or Arm B3 (EBR 50 mg/GZR 100 mg with or without ribavirin for 12 weeks, respectively) and were stratified by genotype. A schematic design for part B of the C-SCAPE trial can be found in Figure 5. Only the treatment arm that included patients with HCV genotypes 4, 5, or 6 who were treated with EBR 50 mg/GZR 100 mg for 12 weeks was included in this review. Other treatment arms were excluded from this review because the regimen used was different from the Health Canada–approved regimen.

**FIGURE 5: TRIAL DESIGN OF C-SCAPE STUDY**




EBR = elbasvir; GT = genotype; GZR = grazoprevir; RBV = ribavirin; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; TW = treatment week.
Source: Clinical Study Reports: C-SCAPE.[19]

### 3.2.2 Populations

#### a) Inclusion and Exclusion Criteria

The main inclusion and exclusion criteria for the included trials are summarized in Table 7. The included trials recruited adult patients with CHC infection, with HCV RNA levels ≥ 10,000 IU/mL at the time of screening. The trials enrolled adults with CHC genotypes 1, 4, or 6 (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-EDGE Treatment-Experienced), genotype 1 (C-SURFER, C-SALVAGE), genotype 1 or 3 (C-SWIFT, C-WORTHY), or genotypes 2, 4, 5, or 6 (C-SCAPE).

Four trials enrolled patients who were treatment-naive (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SWIFT, C-SCAPE); two trials included treatment-experienced patients (C-EDGE Treatment-Experienced, C-SALVAGE); and two trials included treatment-naive and treatment-experienced patients (C-SURFER, C-WORTHY). In the C-EDGE Treatment-Experienced study, the treatment-experienced patients had a prior null, partial response or relapse to PR, while in the C-SALVAGE study, the treatment-experienced patients had prior non-response, breakthrough, or relapse to PR + DAA. In the C-SURFER study, the treatment-experienced patients had prior interferon or PR treatment failures null response, partial response, or relapse. Patients included in the C-EDGE Coinfection study had to be coinfected with HIV, and patients included in the C-SURFER study had to have CKD, defined as patients with GFR ≤ 29 mL/min who were non-dialysis dependent (NDD) or had been on hemodialysis (HD) for at least three months (including patients awaiting kidney transplant and patients with failed kidney transplants no longer on immunosuppressant therapy).

All trials excluded patients with decompensated liver disease, hepatitis B coinfection, malignancy, prior organ transplant (in all studies except the C-SURFER trial, in which patients with prior kidney transplant were included in the trial), or recent substance abuse. The C-EDGE Treatment-Naive, C-SURFER, C-SWIFT, C-SALVAGE and C-SCAPE trials excluded patients coinfected with HIV. Only the C-SCAPE trial excluded patients with cirrhosis, while the rest of the trials included both cirrhotic and non-cirrhotic patients.

**b) Baseline Characteristics**

Across the studies, the mean age ranged from 42 to 59 years of age, the proportion of males ranged from 42% to 100%, and the proportion of patients of white race ranged from 43% to 100% (Table 8). In the trials that allowed cirrhotic patients to be included, the proportion of patients with cirrhosis (or METAVIR fibrosis stage F4) varied between cohorts within trials and between trials (range 6% to 100%); however, the baseline characteristics between the randomized treatment groups in the C-EDGE Treatment-Naive, C-SURFER, and C-EDGE Treatment-Experienced trials appear to be similar. As most studies were non-randomized, differences between treatment groups within the same trial are expected. The C-EDGE Treatment-Experienced trial included patients with previous exposure to PR; the majority of patients were non-responders to this treatment (range 41% to 47%), which was followed by the relapsers (33% to 38%), with partial responders the least represented (20% to 22%). In the C-SURFER study, the majority of patients were on dialysis (range 55% to 77%), had stage 5 CKD (range 64% to 84%), and the proportion of prior renal transplant failures ranged from 14% to 25%. In addition, in the C-SURFER study, baseline values for hemoglobin (Hgb) in the treatment group (mean 120 g/L, median 119 g/L, range 82 to 168 g/L) were comparable to those in the placebo group (mean 118 g/L, median 118 g/L, range 88 to 168 g/L).

**TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS**

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11) | EBR/GZR for 12 Weeks (n = 111) | PBO 12 Weeks (n = 113) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12) |
| **Age, mean (SD)** | 52.2 (11.1) | 53.8 (11.2) | 48.7 (8.9) | 58.2 (6.8) | 56.5 (9.1) | 55.2 (10.1) | 55.7 (9.8) | 55.0 (9.6) | 42.2 (11.7) | 55.3 (5.3) |
| **Male, n (%)** | 171 (54.1) | 56 (53.3) | 183 (83.9) | 11 (100.0) | 81 (73.0) | 80 (70.8) | 66 (62.9) | 64 (60.4) | 8 (57.1) | 10 (83.3) |
| **Race, n (%)** | | | | | | | | | | |
| White | 191 (60.4) | 73 (69.5) | 167 (76.6) | 6 (54.5) | 55 (49.5) | 48 (42.5) | 66 (62.9) | 78 (73.6) | 14 (100) | 12 (100) |
| Black or African-American | 59 (18.7) | 18 (17.1) | 38 (17.4) | 5 (45.5) | 50 (45.0) | 53 (46.9) | 23 (21.9) | 15 (14.2) | 0 | 0 |
| Asian | 54 (17.1) | 13 (12.4) | 6 (2.8) | 0 | 5 (4.5) | 9 (8.0) | 15 (14.3) | 10 (9.4) | 0 | 0 |
| Other | 12 (3.8) | 1 (1.0) | 7 (3.2) | 0 | 1 (0.9) | 3 (2.7) | 1 (1.0) | 3 (2.8) | 0 | 0 |
| **HCV genotype, n (%)** | | | | | | | | | | |
| Genotype 1a | 157 (49.7) | 54 (51.4) | 144 (66.1) | 10 (90.9) | 53 (47.7) | 59 (52.2) | 61 (58.1) | 58 (54.7) | NA | NA |
| Genotype 1b | 131 (41.5) | 40 (38.1) | 44 (20.2) | 1 (9.1) | 58 (52.3) | 53 (46.9) | 34 (32.4) | 36 (34.0) | NA | NA |
| Genotype 1 other | 0 | 0 | 1 (0.5) | 0 | 0 | 1 (0.9) | 1 (1.0) | 2 (1.9) | NA | NA |
| Genotype 3 | NA | NA | NA | NA | NA | NA | NA | NA | 14 (100) | 12 (100) |
| Genotype 4 | 18 (5.7) | 8 (7.6) | 28 (12.8) | NA | NA | NA | 9 (8.6) | 8 (7.5) | NA | NA |
| Genotype 6 | 10 (3.2) | 3 (2.9) | 1 (0.5) | NA | NA | NA | 0 | 2 (1.9) | NA | NA |
| **Baseline HCV RNA** | | | | | | | | | | |
| $log_{10}$ IU/mL, mean (SD) | 6.4 (6.5) | 6.4 (6.5) | 6.03 (0.57) | NR | NR | NR | NR | NR | 5.78 (0.84) | 6.20 (0.40) |
| > 800 000 IU/mL | 222 (70.3) | 66 (62.9) | 127 (58.3) | 8 (72.7) | 61 (55.0) | 66 (58.4) | 84 (80.0) | 73 (68.9) | 6 (42.9) | 8 (66.7) |
| **Prior treatment status** | | | | | | | | | | |
| Treatment-naive | 316 (100) | 105 (100) | 218 (100) | 10 (90.9) | 91 (82.0) | 88 (77.9) | 0 | 0 | 14 (100) | 12 (100) |
| Treatment-experienced | NA | NA | NA | 1 (9.1) | 20 (18.0) | 2 5 (22.1 ) | 105 (100) | 106 (100) | NA | NA |

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** | **EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14)** | **EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12)** |
| **Previous response to PR treatment** | | | | | | | | | | |
| Non-responder (null responder) | NA | NA | NA | NR | NR | NR | 49 (46.7) | 43 (40.6) | NA | NA |
| Partial responder | NA | NA | NA | NR | NR | NR | 21 (20.0) | 23 (21.7) | NA | NA |
| Relapser | NA | NA | NA | NR | NR | NR | 35 (33.3) | 40 (37.7) | NA | NA |
| **Interferon eligible, yes [n, (%)]** | 310 (98.1) | 102 (97.1) | NR | NR | NR | NR | NR | NR | NR | NR |
| **METAVIR score** | | | | | | | | | | |
| F0 to F2 | 210 (66.5) | 69 (65.7) | 160 (73.4) | 11 ( 100.0) | 76 (68.5) | 76 (67.3) | 49 (46.7) | 56 (52.8) | 11 (78.6) | 0 |
| F3 | 36 (11.4) | 14 (13.3) | 23 (10.6) | 0 | 13 (11.7) | 15 (13.3) | 19 (18.1) | 13 (12.3) | 3 (21.4) | 0 |
| F4 | 70 (22.2) | 22 (21.0) | 35 (16.1) | 0 | 7 (6.3) | 7 (6.2) | 37 (35.2) | 37 (34.9) | 0 | 12 (100) |
| No evidence of cirrhosis by FibroTest Score | 0 | 0 | 0 | 0 | 15 (13.5) | 15 (13.3) | 0 | 0 | 0 | 0 |
| **HCV/HIV coinfection, yes [n, (%)]** | NA | NA | 218 (100) | NA | NA | NA | 6 (5.7) | 4 (3.8) | NA | NA |
| **Dialysis Status** | | | | | | | | | | |
| On Dialysis | NR | NR | NR | 6 (54.5) | 86 (77.5) | 87 (77.0) | NR | NR | NR | NR |
| Not On Dialysis | NR | NR | NR | 5 (45.5) | 25 (22.5) | 26 (23.0) | NR | NR | NR | NR |
| **Chronic kidney disease stages** | | | | | | | | | | |
| Stage 4 | NA | NA | NA | 4 (36.4) | 18 (16.2) | 22 (19.5) | NR | NR | NR | NR |
| Stage 5 | NA | NA | NA | 7 (63.6) | 93 (83.8) | 91 (80.5) | NR | NR | NR | NR |
| **Prior renal transplant failure, yes [n, (%)]** | NA | NA | NA | 2 (18.2) | 15 (13.5) | 28 (24.8) | NA | NA | NA | NA |
| **Baseline eGFR (mL/min/1.73m[2])** | | | | | | | | | | |
| Mean (SD) | 108.48 (28.35) | 106.14 (27.26) | NR | 14.3 (7.3) | 10.7 (6.6) | 11.5 (8.0) | NR | NR | NR | NR |

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** | **EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14)** | **EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12)** |
| Range | 51.0 to 364.0 | 48.0 to 175.0 | NR | 5.0 to 26.0 | 4.0 to 38.0 | 3.0 to 43.0 | NR | NR | NR | NR |

EBR = elbasvir; eGFR = estimated glomerular filtration rate; GZR = grazoprevir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NA = not applicable; NR = not reported; NT = PBO = placebo; PK = pharmacokinetic; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RNA = ribonucleic acid; SD = standard deviation; SOF = sofosbuvir.
Source: Zeuzem et al.;[33] Rockstroh et al.;[34] Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS, CONTINUED**

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT1b: EBR/GZR for 12 Weeks (n = 13)** | **TN NC GT1a: EBR/GZR for 12 Weeks (n = 31)** | **TN NC GT1b: EBR/GZR for 8 Weeks (n = 31)** | **TN HIV NC GT1: EBR/GZR for 12 Weeks (n = 30)** | **TN C GT1: EBR/GZR for 12 Weeks (n = 29)** | **Null responder GT1: EBR/GZR for 12 Weeks (n = 33)** | **EBR/GZR+ RBV for 12 Weeks (n = 79)** | **EBR/GZR for 12 Weeks (n = 19)** |
| **Age, mean (SD)** | 43.3 (13.5) | 53.6 (8.4) | 55.3 (10.3) | 43.5 (10.4) | 59.0 (7.8) | 54.4 (9.1) | 54.4 (9.6) | 52.8 (12.3) |
| **Male, n (%)** | 7 (53.8) | 16 (51.6) | 13 (41.9) | 24 (80.0) | 19 (65.5) | 20 (60.6) | 46 (58.2) | 12 (63.2) |
| **Race, n (%)** | | | | | | | | |
| White | 9 (69.2) | 27 (87.1) | 25 (80.6) | 24 (80.0) | 28 (96.6) | 32 (97.0) | 77 (97.5) | 13 (68.4) |
| Black or African-American | 3 (23.1) | 2 (6.5) | 6 (19.4) | 4 (13.3) | 1 (3.4) | 1 (3.0) | 2 (2.5) | 1 (5.3) |
| Asian | 1 (7.7) | 0 | 0 | 1 (3.3) | 0 | 0 | 0 | 5 (26.3) |
| Other | 0 | 2 (6.5) | 0 | 1 (13.3) | 0 | 0 | 0 | 0 |
| **HCV genotype, n (%)** | | | | | | | | |
| Genotype 1a | 0 | 30 (96.8) | 0 | 22 (73.3) | 20 (69.0) | 22 (66.7) | 30 (38.0) | 1 (5.3) |
| Genotype 1b | 13 (100) | 1 (3.2) | 31 (100) | 8 (26.7) | 7 (24.1) | 11 (33.3) | 49 (62.0) | NA |
| Genotype 1 other | 0 | 0 | 0 | 0 | 2 (6.9) | 0 | 0 | NA |
| Genotype 3 | NA | NA | NA | NA | NA | NA | 0 | NA |
| Genotype 4 | NA | NA | NA | NA | NA | NA | 0 | 10 (52.6) |

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT1b: EBR/GZR for 12 Weeks (n = 13)** | **TN NC GT1a: EBR/GZR for 12 Weeks (n = 31)** | **TN NC GT1b: EBR/GZR for 8 Weeks (n = 31)** | **TN HIV NC GT1: EBR/GZR for 12 Weeks (n = 30)** | **TN C GT1: EBR/GZR for 12 Weeks (n = 29)** | **Null responder GT1: EBR/GZR for 12 Weeks (n = 33)** | **EBR/GZR+ RBV for 12 Weeks (n = 79)** | **EBR/GZR for 12 Weeks (n = 19)** |
| Genotype 6 | NA | NA | NA | NA | NA | NA | 0 | 4 (21.1) |
| **Baseline HCV RNA** | | | | | | | | |
| log10 IU/mL, mean (SD) | 6.16 (0.55) | 6.49 (0.54) | 6.65 (0.62) | 6.36 (0.99) | 6.43 (0.61) | 6.67 (0.42) | 6.1 (0.5) | 6.4 (0.6) |
| > 800 000 IU/mL | 7 (53.8) | 26 (83.9) | 27 (87.1) | 25 (83.3) | 25 (86.2) | 32 (97.0) | 50 (63.3) | 14 (73.7) |
| **Prior treatment status** | | | | | | | | |
| TN | 13 (100) | 31 (100) | 31 (100) | 30 (100) | 29 (100) | NA | NA | 19 (100( |
| TE | NA | NA | NA | NA | NA | 33 (100) | 79 (100) | NA |
| Non-responder | NA | NA | NA | NA | NA | 33 (100) | 16 (20.3)[a] | NA |
| Partial responder | NA | NA | NA | NA | NA | NA | NR | NA |
| Relapser | NA | NA | NA | NA | NA | NA | 26 (32.9)[a] | NA |
| **Previous DAA received** | | | | | | | | |
| Boceprevir | NA | NA | NA | NA | NA | NR | 28 (35.4) | NA |
| Telaprevir | NA | NA | NA | NA | NA | NR | 43 (54.4) | NA |
| Simeprevir | NA | NA | NA | NA | NA | NR | 8 (10.1) | NA |
| **METAVIR score** | | | | | | | | |
| F0-F2 | 13 (100) | 26 (83.9) | 29 (93.5) | 27 (90.0) | 0 | 16 (48.5) | 37 (46.8) | 17 (89.5) |
| F3 | 0 | 5 (16.1) | 2 (6.5) | 3 (10.0) | 0 | 3 (9.1) | 8 (10.1) | 1 (5.3) |
| F4 | 0 | 0 | 0 | 0 | 29 (100) | 14 (42.4) | 34 (43.0) | 0 |
| **HCV/HIV coinfection, yes [n, (%)]** | NA | NA | NA | 30 (100) | NA | NA | NA | NA |

C = cirrhotic; DAA = direct-acting antiviral agent; EBR = elbasvir; GT = genotype; GZR = grazoprevir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NA = not applicable; NR = not reported; NC = non-cirrhotic; RNA = ribonucleic acid; SD = standard deviation; TE = treatment-experienced; TN = treatment-naive.

[a] Previous response to DAA treatment.

Source: Clinical Study Reports: C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE.[20]

### 3.2.3 Interventions

Table 9 provides a listing of the treatment regimens administered by study population. In all trials, the dose of GZR was 100 mg and the dose of EBR was 50 mg (12 weeks for all trials except for the C-EDGE Treatment-Experienced trial, in which patients received 12 or 16 weeks of treatment). In the C-SALVAGE and C-EDGE Treatment-Experienced studies, patients also received weight-based ribavirin (< 66 kg = 800 mg/day, 66 to 80 kg = 1,000 mg/day, 81 to 105 kg = 1,200 mg/day, > 105 kg = 1,400 mg/day) administered in two divided doses with food (12 weeks in C-SALVAGE and 16 weeks in C-EDGE Treatment-Experienced). In the C-SWIFT study, patients also received sofosbuvir 400 mg daily for 12 weeks.

In the C-EDGE Treatment-Naive and C-SURFER trials, patients were randomized to receive either EBR 50 mg/GZR 100 mg or identically packaged placebo for 12 weeks to examine treatment-related harms. Patients in the placebo treatment group received placebo for 12 weeks followed by four weeks of follow-up and then 12 weeks of open-label treatment with EBR 50 mg/GZR 100 mg.

### 3.2.4 Outcomes

Outcome measures were consistent among the included trials. The primary efficacy outcome measure was the proportion of patients achieving SVR12, defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after the end of all study therapy.

Relapse was defined as having a confirmed HCV RNA ≥ LLOQ following end of all study therapy, after becoming undetectable at the end of treatment. Confirmation is defined as an HCV RNA ≥ LLOQ from a separate blood draw repeated within two weeks.

Health-related quality of life (HRQoL) assessments were performed frequently throughout the trial and in post-treatment follow-up. HRQoL was assessed in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials using the Chronic Liver Disease Questionnaire (CLDQ), which is an HRQoL instrument for patients with chronic liver disease. CLDQ-HCV measures Activity/Energy, Emotion, Worry, Systemic, and CLDQ-HCV total score. Scores are based on a Likert scale from 0 (worst) to 7 (best). A minimal clinically important difference (MCID) for CLDQ-HCV has not been estimated. Only patients enrolled at sites in the US, and whose native language was either English or Spanish, were eligible to complete the CLDQ-HCV.

The C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials also employed the Short Form 36-Item Health Survey (SF-36), and the EuroQol Visual Analogue Scale (EQ VAS) to assess HRQoL. The trials also employed the Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-F) and the Work Productivity and Activity Impairment (WPAI) questionnaire, to assess fatigue, and productivity and impairment, respectively. SF-36 was also employed in the C-SURFER trial.

**TABLE 9: ELBASVIR/GRAZOPREVIR TREATMENT REGIMEN BY POPULATION AND STUDY**

| Genotype/ Prior Treatment Exposure | Treatment Regimen[a] | | | | |
|---|---|---|---|---|---|
| | EBR/GZR 8 Weeks[b] | EBR/GZR 12 Weeks[c] | EBR/GZR 12 Weeks + RBV | EBR/GZR 16 Weeks + RBV[d] | EBR/GZR + SOF 12 Weeks[e] |
| **TN** | | | | | |
| 1a | | C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, C-WORTHY | | | |
| 1b | C-WORTHY | C-EDGE Treatment-Naive, | | | |

| Genotype/ Prior Treatment Exposure | Treatment Regimen[a] | | | | |
|---|---|---|---|---|---|
| | **EBR/GZR 8 Weeks[b]** | **EBR/GZR 12 Weeks[c]** | **EBR/GZR 12 Weeks + RBV** | **EBR/GZR 16 Weeks + RBV[d]** | **EBR/GZR + SOF 12 Weeks[e]** |
| | | C-EDGE Coinfection, C-SURFER, C-WORTHY | | | |
| 3 | | | | | C-SWIFT |
| 4 | | C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SCAPE | | | |
| **PR-TE[f] relapsers, or PI/PR-TE[g] (for genotype 1 patients) relapsers** | | | | | |
| 1a | | C-SURFER, C-EDGE Treatment-Experienced | C-SALVAGE | C-EDGE Treatment-Experienced | |
| 1b | | C-SURFER, C-EDGE Treatment-Experienced | C-SALVAGE | C-EDGE Treatment-Experienced | |
| 4 | | C-EDGE Treatment-Experienced | | C-EDGE Treatment-Experienced | |
| **PR-TE or PI/PR-TE (for genotype 1 Patients) on-treatment virologic failures[h]** | | | | | |
| 1a | | C-SURFER,[i] C-EDGE Treatment-Experienced, C-WORTHY | C-SALVAGE | C-EDGE Treatment-Experienced | |
| 1b | | C-SURFER, C-EDGE Treatment-Experienced, C-WORTHY | C-SALVAGE | C-EDGE Treatment-Experienced | |
| 4 | | C-EDGE Treatment-Experienced | | C-EDGE Treatment-Experienced | |

EBR = elbasvir; GZR = grazoprevir; IFN = interferon; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive.

[a] Shaded cells indicate Health Canada–approved dosage regimen. If blank, then no clinical trial data were available for that population and treatment combination.

[b] Eight weeks of EBR/GZR may be considered in TN genotype 1b (Includes patients with known genotype 1 subtypes other than 1a or 1b) patients without significant fibrosis or cirrhosis (as determined by liver biopsy [i.e., METAVIR F0 to F2] or by non-invasive tests).

[c] 12-week EBR/GZR regimen approved for patients with genotype 1 or 4 TN and PR-TE relapsers, in genotype 1 PI/PR-TE relapsers, and in genotype 1b PR- or PI/PR-TE on-treatment virologic failures.

[d] 16-week EBR/GZR + RBV regimen approved for patients with genotype 1a PR- or PI/PR-TE on-treatment virologic failures, and in genotype 4 PR-TE on-treatment virologic failures.

[e] 12-week EBR/GZR + SOF regimen approved for genotype 3 TN patients.

[f] PR-TE: Patients who failed treatment with PR.

[g] PI/PR-TE: Patients who failed PR + boceprevir, simeprevir, or telaprevir.

[h] On-treatment virologic failures are patients who have had a null response, partial response, virologic breakthrough or rebound, or intolerance to prior treatment.

[i] Patients with genotype 1 with severe renal impairment (estimated eGFR < 30 mL/min/1.73 $m^2$) or with end-stage renal disease should receive EBR/GZR12 weeks without ribavirin regardless of prior treatment experience.

The FACIT-F contains 13 items and is scored using a 5-point Likert-type response scale to rate each item, where 0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much with a recall period of "during the past 7 days."[16] Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale (40 items in total), make up the total score, ranging from 0 (worst) to 160 (best).[41] Although no information on the validity of FACIT-F or its MCID in CHC patients was found, the MCID for the FACT-General total score ranged from 3 to 7 points in cancer patients, and the MCID in the FACIT-F ranged from 3 to 4 points in rheumatoid arthritis patients.[42,43]

The WPAI is an instrument used to measure the impact of a disease on work and daily activities. The work impairment domain is the sum of impairment in work productivity due to absenteeism

(productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days) and impairment due to decreased productivity while at work (reduced performance of productivity while at work due to health reasons, including time not spent on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. Four main outcomes can be generated from the WPAI and expressed in percentages: 1) percentage of work time missed due to health for those who were currently employed; 2) percentage of impairment while working due to health for those who were currently employed and actually worked in the past seven days; 3) percentage of overall work impairment due to health for those who were currently employed; 4) percentage of activity impairment due to health for all respondents. For those who missed work and did not actually work in the past seven days, the percentage of overall work impairment due to health will be equal to the per cent work time missed due to health. The scores are presented as a percentage, with lower values indicating better quality of life.[44,45] Although no information on the validity of WPAI or its MCID in CHC patients was found, the MCID for the WPAI has been reported to be ≥ 7 percentage points in patients suffering from Crohn disease.[45]

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. SF-36 consists of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. According to a panel of experts convened to indirectly estimate the MCID in hepatitis C based upon existing HRQoL data, the vitality dimension of the SF-36 was considered most relevant patients with CHC infection.[46] In a systematic review that was conducted to identify and provide information on HRQoL instruments for CHC,[46] it was found that the largest impact of the disease was on role physical, role emotional, and general health. The individual domain scores can be aggregated to create a physical component summary (PCS) and a mental component summary (MCS). Scores for each component range from 0 to 100, with higher scores reflecting better HRQoL. The only information regarding the MCID in patients with CHC was for the SF-36 vitality dimension, for which the MCID was estimated by experts at 4.2 points (range 3 to 5). In general use of SF-36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient.[47] No MCID estimates in patients with CHC were found for the component scores or for domains other than vitality. It is unclear whether the MCID estimates from other conditions or the general population are generalizable to HCV.

The EQ VAS is a 20 cm visual analog scale that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day. Further information regarding the validity of HRQoL instruments employed in the trials can be found in Appendix 5.

### 3.2.5 Harms

An adverse event was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore have been any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the sponsor's product is also an adverse event.

### 3.2.6 Statistical Analysis

In C-EDGE Treatment-Naive trial randomization was stratified by fibrosis stage (non-cirrhotic versus cirrhotic) and HCV genotype or subtype (genotype 1a versus genotype 1 non-a versus genotypes 4 or 6). In the C-SURFER trial, randomization was stratified by hemodialysis status at baseline and by the presence of a diagnosis of diabetes mellitus at baseline. In the C-EDGE Treatment-Experienced trial, randomization was stratified by the presence or absence of cirrhosis and by prior PR treatment response (relapser, partial responder, or null responder). In C-WORTHY, in part A, patients were stratified by HCV genotype (1a versus 1b), and in part B, in the patient population of prior null responders, randomization was stratified by the presence or absence of cirrhosis. In the C-EDGE Treatment-Naive, C-SURFER, and C-EDGE Treatment-Experienced trials, randomization was performed centrally using an interactive voice response system and/or integrated Web response system. In the C-WORTHY trial randomization was performed centrally using an interactive voice system.

In the C-EDGE Treatment-Naive trial, it was estimated that 400 patients need to be randomized with 300 patients in the immediate treatment arm and 100 patients in the deferred arm. The deferred arm served as placebo control for the first 12 weeks, then received open-label active treatment after unblinding at week 16. The primary hypothesis was evaluated for patients in the immediate treatment arm (n = 300). Assuming a response rate of at least 85% in the immediate treatment arm, the study had over 99% power to demonstrate that the SVR12 rate was superior to the historical reference rate of 73% at an overall one-sided 2.5% alpha level. The calculation was based on a z test using the normal approximation to the binomial distribution. The historical reference rate of 73% was derived from the phase 3 trials of simeprevir/PR in treatment-naive, HCV monoinfected patients (QUEST 1 and 2)[48,49] after adjusting for the expected proportion of patients with cirrhosis in the C-EDGE Treatment-Naive study and an expected improved safety profile related to an interferon-free regimen. This approximation was used as the historical reference rate in assessing the primary hypothesis of the study that includes patients with HCV genotypes 4 and 6, in addition to patients with HCV genotype 1. The primary hypothesis was that patients in the immediate treatment arm (which included patients with genotypes 1, 4, and 6) would achieve an SVR12 rate superior to the reference rate of 73%, tested at a one-sided significance level (type I error) of 0.025. A two-sided 95% confidence interval (CI) was also constructed for the SVR12 rate. The SVR12 rate (with a two-sided 95% CI) was estimated for the following subgroups: genotype (1a, 1 non-a, 4 and 6), stage of fibrosis (non-cirrhotic versus cirrhotic), HCV RNA at baseline, low (≤ 800,000 IU/mL) versus high (> 800,000 IU/mL), and interferon treatment eligibility status (eligible or ineligible).

In the C-EDGE Coinfection trial, it was estimated that 200 patients have to be allocated into a single treatment group. Assuming a true response rate of at least 85%, the study had over 99% power to demonstrate that the SVR12 rate was superior to the historical reference rate of 70% at an overall one-sided 2.5% alpha level. The historical reference rate of 70% was derived from the phase 2 trial of sofosbuvir in HCV genotype 1 patients coinfected with HIV (PHOTON-1);[50] after adjusting for the expected higher proportion of patients with cirrhosis in the C-EDGE Coinfection trial, it was estimated that response would be approximately 75%. A 5% decrease was applied to the above response rate because of an expected improved safety profile on EBR/GZR as an interferon-free regimen. This value (SVR12 of 70%) was then used as the historical reference rate in assessing the primary hypothesis. The primary hypothesis was that the proportion of patients receiving EBR/GZR and achieving SVR12 (included patients with genotypes 1, 4, and 6) would be superior to 70%, tested at a one-sided significance level (type I error) of 0.025. The SVR12 rate (with a two-sided 95% CI) was estimated for the following subgroups: genotype (1a, 1b, 1-other, 4, and 6), stage of fibrosis (non-cirrhotic versus

cirrhotic), HCV RNA at baseline, low (≤ 800,000 IU/mL) versus high (> 800,000 IU/mL), interferon treatment eligibility status (eligible or ineligible), and antiretroviral therapy.

In the C-SURFER trial, it was estimated that 105 patients needed to be randomized into the immediate treatment arm and 105 patients into the deferred treatment group. In addition, 10 patients were to be enrolled in the intensive PK cohort. The primary hypothesis was evaluated for patients from the combined immediate treatment and the intensive PK arms (n = 115). Assuming the true SVR12 rate of EBR/GZR is approximately 65%, there would be at least 95% power to demonstrate that the SVR12 rate of GZR + EBR is higher than the historical reference SVR12 rate of 45% at an overall one-sided 0.025 alpha level. Several considerations led to the choice of a reference SVR of 45%, including guidelines for HCV-infected patients with CKD stages 3 to 5,[51] a meta-analysis on interferon monotherapy of chronic hepatitis C in dialysis patients that produced an SVR24 of 39%, 95% CI (32% to 46%),[52] and a clinical trial that reported that the SVR of approximately 40% was observed in a large study of PR in 3,070 HCV genotype 1 patients without CKD,[53] and that the SVR response of patients with CKD stages 4 or 5 was not expected to be higher than that of the general HCV population without CKD. The primary hypothesis was that patients treated with EBR/GZR for 12 weeks would achieve an SVR12 rate higher than the reference SVR12 rate of 45%. This hypothesis was evaluated for patients in the immediate treatment and the intensive PK arms combined, and it was tested at a two-sided significance level (type I error) of 0.05. A 95% CI was also constructed for the SVR12 rate. The SVR12 rate and associated 95% CI were estimated for the following subgroups: genotype (1a versus 1 non-a); stage of fibrosis (non-cirrhotic versus cirrhotic); HCV RNA at baseline, low (≤ 800,000 IU/mL) versus high (> 800,000 IU/mL); dialysis (yes versus no); diabetes (yes versus no); CKD stage (4 versus 5); and prior interferon or PR treatment response (treatment-naive, relapser, partial responder, and null responder).

In the C-EDGE Treatment-Experienced trial, it was estimated that 400 patients needed to be allocated into four arms in a 1:1:1:1 ratio. There was 99% power to demonstrate the primary hypothesis that the proportion of patients in at least one of the arms would have an SVR12 rate superior to 58% at an overall 0.05 alpha level. The power calculation is based on the assumption of an underlying response rate of at least 80% in the treatment arms. The minimum number of patients needed to achieve SVR12 and satisfy the criterion for the primary efficacy hypothesis in an arm is 69 out of 100 patients (69%). The historical reference rate of 58% is derived from a phase 2b registration trial of simeprevir (100 mg or 150 mg once daily) for 12, 24, or 48 weeks in combination with PR for 48 weeks in treatment-experienced patients.[54] Adjustments were made for the expected proportion of patients who were null and partial responders in the C-EDGE Treatment-Experienced trial and an expected improved safety profile related to an interferon-free regimen. The 58% was used as the historical reference rate in assessing the primary hypothesis of the study for patients with HCV genotypes 1, 4, and 6. The primary hypothesis compared SVR12 in each treatment arm (including patients with genotypes 1, 4, and 6) with a historical reference rate of 58% using an exact test for binomial proportions (at a one-sided alpha level of 0.0125 to control for multiplicity) with a Missing = Failure approach for missing values. A two-sided 95% CI based on the Clopper-Pearson method was also provided for each treatment arm. The SVR12 rate and associated 95% CI were estimated for the following subgroups: genotype (1a, 1 non-a, 4, and 6); stage of fibrosis (non-cirrhotic versus cirrhotic); HCV RNA at baseline, low (≤ 800,000 IU/mL) versus high (> 800,000 IU/mL); prior treatment response (relapser, partial responder, and null responder); and HCV/HIV coinfected versus HCV monoinfected.

No sample size calculation was undertaken for the C-SWIFT, C-WORTHY, C-SALVAGE, and C-SCAPE trials.

In the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, C-EDGE Treatment-Experienced, and C-SWIFT trials, a missing data point for a given study visit may be due to any one of the following reasons: a visit occurred but data were not collected or were unusable; a visit did not occur; or a patient discontinued from the study before reaching the visit. Patients who prematurely discontinued the assigned treatment were encouraged to remain in the study for the follow-up, if possible. There were three types of missing data handled by different approaches:

1. Intermittent missing: If a missing data point was immediately preceded and followed by non-missing HCV RNA outcomes, the missing value would be imputed to the worst outcome of the two.
2. Non-intermittent missing related to the study drug: For values missing due to premature study discontinuations for treatment-related reasons, either for safety or efficacy, the missing values were considered as treatment failures.
3. Non-intermittent missing unrelated to the study drug: For missing data due to premature study discontinuations with reasons unrelated to treatment — such as lost to follow-up, protocol violation, withdrawal of consent, administrative reasons, etc. — the mechanism for missing data is unlikely to be related to patients' response to the HCV treatment, and therefore the missing at random (MAR) assumption is reasonable. The approaches to address this type of missing data depend on the analytical strategy, and they are described as follows:
    - Treatment-Related Discontinuation = Failure (TRD=F) approach: The treatment related to missing data type 2 was considered a failure, whereas patients who had the missing data type 3 and did not have virologic failure during the observed study period were excluded from the analysis for the time points following their study withdrawal. Patients with documented virologic failure during the treatment or follow-up period, even if they withdrew prematurely due to reasons not related to study drug, were classified as failures. This approach was used for the per-protocol (PP) analysis in the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, C-EDGE Treatment-Experienced, and C-SWIFT trials. It was also used in the modified full analysis set (mFAS) in C-SURFER trial.
    - Missing=Failure (M=F) approach: Any non-intermittent missing (i.e., type 2 and 3 missing data) was imputed as failure, regardless of the reason for study discontinuation. This approach was used for the full analysis set (FAS) analysis in the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, C-EDGE Treatment-Experienced, and C-SWIFT trials.

In the C-WORTHY, C-SALVAGE, and C-SCAPE trials, the missing = failure approach was used for the FAS population, where any patient missing an HCV RNA evaluation at any particular visit was considered a non-responder for that visit. An exception was made in the case where a missing on-treatment visit was immediately preceded and followed by an HCV RNA not detected, where the missing value was imputed to be HCV RNA not detected as well. The same rule was applied when the end point is defined using HCV RNA < LLOQ. When a missing value was flanked by HCV RNA not detected and HCV RNA< LLOQ, then HCV RNA < LLOQ was imputed. The Observed Failure (OF) approach was used for the PP population where patients who 1) discontinued assigned treatment early due to lack of efficacy or 2 discontinued from the study following a confirmed HCV RNA ≥ LLOQ during follow-up were considered as failures thereafter. Otherwise, any patient missing an HCV RNA evaluation at any particular visit was excluded from the analysis at that time point.

In the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, and C-EDGE Treatment-Experienced trials, the patient-reported outcome (PRO) scores (CLDQ-HCV, FACIT-F, WPAI, SF-36, and EQ VAS in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials and SF-36 in the C-SURFER trial) and the change from baseline in each of the PRO scores were summarized by

treatment groups and by the time points. If a patient discontinued, the PRO completed at the discontinuation visit was mapped to the nearest analysis time point. Missing data were not imputed, and the analysis was based on observed data only (DAO approach). The estimation of mean PRO scores included all available data at each time point. To investigate the treatment effect on PRO scores within each treatment group, (e.g., whether mean change from baseline is different than 0), mean change from baseline in PRO scores, with the corresponding 95% CI, were estimated for on-treatment and follow-up time points. To investigate differences between treatment groups, differences in mean change from baseline in PRO scores between treatment groups with the corresponding 95% CI for the treatment difference were estimated for on-treatment and follow-up time points. No adjustment for baseline covariates was made in the analysis of differences in mean change from baseline and in the difference between treatment groups. Patients had to have PRO scores both at baseline and at post-baseline time points to be included in the analyses. No formal hypothesis testing was applied considering the exploratory nature of this analysis. Missing values in the HRQoL data in the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, and C-EDGE Treatment-Experienced trials were not imputed.

**a) Analysis Populations**

The FAS population consisted of all randomized, enrolled, or allocated patients who had received at least one dose of study treatment.

The PP population is a subset of the FAS population. The PP population excluded patients due to important deviations from the protocol that may substantially affect the results of the primary and key secondary efficacy end points.

The mFAS population is a subset of the FAS population with patients who were randomized to the immediate treatment arm or who were assigned to the intensive PK arm, with patients excluded for the following reasons: failure to receive at least one dose of active study treatment; data missing due to death with reasons unrelated to study drug or reasons other than liver disease; and data missing due to study discontinuation with reasons unrelated to progression of liver disease, study drug, and their responses to the HCV treatment. The mFAS was only used in the C-SURFER trial.

The safety data were based on all patients as treated population.

In the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials, the FAS population served as the primary population for the analysis of efficacy data.

In C-SURFER, the mFAS population served as the primary population for the analysis of efficacy data.

In C-SWIFT, C-WORTHY, C-SALVAGE, and C-SCAPE, the PP population served as the primary population for the analysis of efficacy data.

## 3.3 Patient Disposition

Between 10.2% and 31.1% of patients enrolled in the trials did not enter the treatment phase; the most common reason stated for this was that the patient did not meet the inclusion criteria (Table 10). Discontinuation rates were low in most of the trials, with the proportion of patients who discontinued the study ranging between 0% and 10%, and the proportion of patients who discontinued study medication ranging from 0% to 10.5%. The highest discontinuation rate was in the C-SURFER trial, which included patients with CKD. Only one to three patients discontinued the C-WORTHY and C-SCAPE trials, but given the small sample sizes, they represent a large proportion.

**TABLE 10: PATIENT DISPOSITION**

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced[a] | | C-SWIFT | |
| | **EBR/GZR for 12 Weeks** | **PBO 12 Weeks** | **EBR/GZR for 12 Weeks** | **EBR/GZR for 12 Weeks (Not Randomized [PK Arm])** | **EBR/GZR for 12 Weeks** | **PBO 12 Weeks** | **EBR/ GZR for 12 Weeks** | **EBR/ GZR + RBV for 16 Weeks** | **EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients)** | **EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients)** |
| **Screened, N** | 469 | | 261 | 328 | | | 482 | | 162 | |
| **Randomized, N** | 421 | | 218 | 237 | | | 420 | | 143 | |
| **Enrolled, N** | 316 | 105 | 218 | 11 | 112 | 114 | 105 | 106 | 14 | 12 |
| **Discontinued study, N (%)** | 3 (0.9) | 2 (1.9) | 2(0.9) | 0 | 7 (6.3) | 11 (9.6) | 3 (2.9) | 1 (0.9) | 0 | 1 (8.3) |
| Death | 2 (0.6) | 0 | 0 | 0 | 1 (0.9) | 4 (3.5) | 1 (1.0) | 0 | 0 | 0 |
| Lost to follow-up | 1 (0.3) | 0 | 0 | 0 | 2 (1.8) | 1 (0.9) | 0 | 1 (0.9) | 0 | 0 |
| Withdrawal by patient | 0 | 2 (1.9) | 0 | 0 | 1 (0.9) | 2 (1.8) | 2 (1.9) | 0 | 0 | 1 (8.3) |
| Status not recorded | 0 | 0 | 2(0.9) | 0 | 0 | 0 | 0 | 1 (0.9) | 0 | 0 |
| Adverse event | 0 | 0 | 0 | 0 | 0 | 4 (3.5) | 0 | 0 | 0 | 0 |
| Non-compliance with study drug | 0 | 0 | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 | 0 |
| Physician decision | 0 | 0 | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 | 0 |
| Screen failure | 0 | 0 | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 | 0 |
| **Discontinued study medication, N (%)** | 5 (1.6) | 1 (1.0) | 1 (0.5) | 0 | 5 (4.5) | 6 (5.3) | 1 (1.0) | 5 (4.7) | 0 | 1 (8.3) |
| Adverse event | 3 (0.9) | 1 (1.0) | 0 | 0 | 0 | 5 (4.4) | 1 (1.0) | 4 (3.8) | 0 | 0 |
| Death | 1 (0.3) | 0 | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 | 0 |
| Kidney transplant | 0 | 0 | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 | 0 |

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced[a] | | C-SWIFT | |
| | **EBR/GZR for 12 Weeks** | **PBO 12 Weeks** | **EBR/GZR for 12 Weeks** | **EBR/GZR for 12 Weeks (Not Randomized [PK Arm])** | **EBR/GZR for 12 Weeks** | **PBO 12 Weeks** | **EBR/ GZR for 12 Weeks** | **EBR/ GZR + RBV for 16 Weeks** | **EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients)** | **EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients)** |
| Lost to follow-Up | 1 (0.3) | 0 | 0 | 0 | 1 (0.9) | 1 (0.9) | 0 | 0 | 0 | 0 |
| Protocol violation | 0 | 0 | 1 (0.5) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Non-compliance with study drug | 0 | 0 | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 | 1 (8.3) |
| Withdrawal by patient | 0 | 0 | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 | 0 |
| Physician decision | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.9) | 0 | 0 |
| **FAS, N** | 316 | NA | 218 | 122 | | NA | 105 | 106 | 14 | 12 |
| **mFAS** | NA | NA | NA | 116[b] | | NA | NA | NA | NA | NA |
| **PP, N** | 313 | NA | 214 | 115 | | NA | 102 | 101 | 14 | 11 |
| **Safety, N** | 316 | 105 | 218 | 11 | 111 | 113 | 105 | 106 | 14 | 12 |

EBR = elbasvir; FAS = full analysis set; GZR = grazoprevir; HCV = hepatitis C virus; mFAS = modified full analysis set; PBO = placebo; PK = pharmacokinetic; PP = per-protocol; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir.

[a] Two treatment arms not reported in this review, as they do not match the approved indication.

[b] Includes all patients who were enrolled and received at least 1 dose of GZR + EBR. It excludes patients with missing HCV RNA results due to premature study discontinuation unrelated to study medication or progression of liver disease.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 10: PATIENT DISPOSITION, CONTINUED**

| | C-WORTHY[a] | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT 1b: EBR/GZR for 12 Weeks** | **TN NC GT 1a: EBR/GZR for 12 Weeks** | **TN HIV NC GT 1: EBR/GZR for 12 Weeks** | **TN C GT 1: EBR/GZR for 12 Weeks** | **Null responder GT 1: EBR/GZR for 12 Weeks** | **TN NC GT 1b: EBR/GZR for 8 Weeks** | **EBR/GZR + RBV for 12 Weeks** | **EBR/GZR for 12 Weeks** |
| **Screened, N** | 106 | 406 | | | | 74 | 97 | 92 |
| **Randomized/allocated, N** | 65 | 94 | 59 | 123 | 130 | 61 | | 68 |
| **Enrolled, N** | 13 | 31 | 30 | 29 | 33 | 31 | 79 | 19 |
| **Discontinued study, N (%)** | 0 | 0 | 3 (10.0) | 0 | 0 | 0 | 1 (1.3) | 1 (5.3) |
| Lost to follow-up | 0 | 0 | 2 (6.7) | 0 | 0 | 0 | 0 | 1 (5.3) |
| Withdrawal by patient | 0 | 0 | 1 (3.3) | 0 | 0 | 0 | 1 (1.3) | 0 |
| **Discontinued study medication, N (%)** | 0 | 0 | 3 (10.0) | 0 | 0 | 0 | 1 (1.3) | 2 (10.5) |
| Lack of efficacy | 0 | 0 | 2 (6.7) | 0 | 0 | 0 | 0 | 1 (5.3) |
| Adverse event | 0 | 0 | | 0 | 0 | 0 | 1 (1.3) | 1 (5.3) |
| Lost to follow-up | 0 | 0 | 1 (3.3) | 0 | 0 | 0 | 0 | 0 |
| **FAS, N** | 13 | 31 | 30 | 29 | 33 | 31 | 79 | 19 |
| **PP, N** | 12 | 31 | 28 | 29 | 33 | 31 | 70 | 13 |
| **Safety, N** | 12 | 31 | 30 | 29 | 33 | 31 | 79 | 19 |

C = cirrhotic; DAA = direct-acting antiviral agent; EBR = elbasvir; GT = genotype; GZR = grazoprevir; HIV = human immunodeficiency virus; NC = non-cirrhotic; RBV = ribavirin; TN = treatment-naive.

[a] Not all treatment arms have been reported in this review, as they do not meet the approved indication.

Source: Clinical Study Reports: C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE.[20]

## 3.4 Exposure to Study Treatments

In the C-EDGE Treatment-Naive trial, 310 (98.1%) of 316 patients completed 12 weeks (± 7 days) of treatment with EBR/GZR, with a mean duration of 84.4 days. In C-EDGE Coinfection, 206 (94.5%) of 218 patients received EBR/GZR for the intended duration of more than 11 weeks and less than 13 weeks, with a mean duration of 84.9 days. In the C-SURFER trial, 113 (92.6%) of 122 patients completed 12 weeks (± 7 days) of treatment with GZR, with a mean duration of 82.8 days, and 114 (93.4%) of 122 patients completed 12 weeks (± 7 days) of treatment with EBR, with a mean duration of 82.9 days. In the C-EDGE Treatment-Experienced trial, the treatment extent of exposure was not well reported; however, it seems that the majority of patients received the appropriate dosing, where seven patients discontinued the study before completing 12 weeks of treatment and overall, 26 patients reported an accidental overdose of EBR/GZR. In the C-SWIFT trial, 25 (96.2) of 26 patients completed the assigned 12-week treatment. The extent of exposure in C-WORTHY was not well documented. In the C-SALVAGE trial, 77 (97.5) of 79 patients completed 12 weeks (± 7 days) of treatment with EBR/GZR, and 76 (96.2) of 79 patients completed 12 weeks (± 7 days) of treatment with RBV. In the C-SCAPE trial, more than 90% of patients received the appropriate duration of therapy.

## 3.5 Critical Appraisal

### 3.5.1 Internal Validity

Randomization and allocation concealment in the C-EDGE Treatment-Naive, C-SURFER, and C-EDGE Treatment-Experienced trials were well reported and shown to be effective based on equitable distribution of baseline characteristics between different treatment arms within each trial. All included trials except C-EDGE Treatment-Naive and C-SURFER were open-label trials; being aware of treatment allocation might have influenced subjective measures, such as HRQoL measures and reporting of adverse events. On the other hand, it is worth noting that in these trials there were placebo data to compare adverse event rates to EBR/GZR.

In all trials, imputation and handling methods used for the missing data for the SVR seem appropriate.

The C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, and C-EDGE Treatment-Experienced trials shared the same limitations related to comparisons with a historical control, rather than a direct comparison between trial arms, which limits the ability to assess differences between the randomized treatments. As historical controls were used as the main comparison, the primary outcome (SVR12 rate) cannot be ascertained directly from the trial. This comparative approach raises several concerns because it compares two cohorts of interventions (i.e., it is essentially an observational study) without a mechanism to ensure that confounders are evenly distributed between groups; thus, there is a higher chance of the observed differences being due to factors other than the evaluated treatments. Also, these trials and the trials from which the historical control rates were derived did not take place in the same time period. This opens the possibility that changes in clinical practice — for example, greater familiarity with the DAAs — may bias the observed treatment differences. In the case of historical control, no guarantee can be made that the patient populations were truly similar aside from the intervention.

Another limitation with the historical control was that in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials tested superiority with an arbitrary reduction in the historical rate of 5% for the anticipated improvement of safety profile related to an interferon-free regimen. In addition, the historical controls used were based on older regimens, which are less efficacious than currently available interferon-free regimens. As well, as the historical control rates are derived from different periods, the standard of care from different time periods may affect results. Finally, the

historical control was based on patients with genotype 1 infection; however, the comparison made included patients with genotype 1, 4, or 6 infections.

Despite the limitations associated with historical comparisons, this trial design for these new drug regimens is accepted by the FDA in the treatment of CHC infection.[55] However, the draft guidance document produced by the FDA noted that future treatments should use alternate study designs with an active control once pegylated interferon–free regimens are available.

No sample size calculation was undertaken for the C-SWIFT, C-WORTHY, C-SALVAGE, and C-SCAPE trials.

In the C-SURFER trial, patients were excluded from the analysis due to the following reasons: failure to receive at least one dose of active study treatment; missing data due to death with reasons unrelated to study drug or reasons other than liver disease; missing data due to study discontinuation with reasons unrelated to progression of liver disease, study drug, and their responses to the HCV treatment. Exclusion of such patients might inflate SVR reported from the primary analysis.

Even though the protocol of the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials indicated that EQ-5D-5L would be carried out, such data were not presented in their respective Clinical Study Reports.

PROs were exploratory efficacy end points and there were no multiplicity adjustments applied to the PRO variables; hence, the results of the PRO (CLDQ-HCV, FACIT-F, WPAI, SF-36, and EQ VAS) should be interpreted with caution, where a statistically significant finding for the comparison for these outcomes is more likely subject to inflated type I error rate (alpha). In addition, there was a lack of data imputation for the PROs data when missing; such missing data are unlikely to be missing at random (usually sicker patients are missing), which could lead to overestimates in HRQoL and/or other PROs. Also, no adjustment for baseline covariates was made in the analysis of differences in mean change from baseline and in the difference between treatment groups. Finally, MCIDs specific to CHC are unknown, which limits the ability to interpret these results.

The intention-to-treat (ITT) population was not used in the analyses; the FAS population, which consisted of all randomized, enrolled, or allocated patients who had received at least one dose of study treatment, was used instead. This FAS population is a modified ITT population.

In C-SWIFT, C-WORTHY, C-SALVAGE, and C-SCAPE, the PP population was used as the primary population for the analysis of efficacy data instead of the ITT population.

### 3.5.2 External Validity

A considerable proportion of patients (0% to 39%) were screened in the trials but did not enter the treatment phase. The most common reason stated was the patient not meeting the inclusion criteria. All trials excluded patients with decompensated liver disease, hepatitis B coinfection, malignancy, and recent substance abuse; therefore, the generalizability of the results of the included studies to these populations is unknown. Furthermore, no data were available on other subgroups of interest, such as patients with liver transplantation. On the other hand, the C-EDGE Coinfection trial included patients who were coinfected with HIV and C-SURFER included patients with CKD; having such patients included in these trials helps improve the generalizability of these results.

There were limited data available in patients with genotypes 4 HCV; the number of patients with genotype 4 enrolled in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced and C-SCAPE trials was small (ranged from eight to 28). Hence, there is uncertainty about whether the SVR rates from the genotype 4 HCV population would be seen in clinical practice. In addition, the characteristics of the study population were not reported by genotype; hence, we are not sure if the patient population with genotype 4 is representative of or similar to the population with genotype 4 in Canada. Only the C-SWIFT trial included patients with genotype 3, and the number of patients included was limited (14 non-cirrhotic patients and 12 cirrhotic patients); therefore, the generalizability of the results is uncertain.

Since all trials included were not actively controlled, the efficacy of EBR/GZR therapy compared with existing treatments cannot be established directly from these studies. The manufacturer did not submit an indirect comparison in order to compare with other regimens, and thus it is difficult to determine the comparative effectiveness and place in therapy, relative to other regimens currently in use in Canada.

In the C-SURFER study, the number of cirrhotic patients (six) and treatment-experienced patients (20) included in this study was small, which might impact the generalizability of results in these subgroups.

The proportion of patients included (in the trial arms that did not include only cirrhotic patients) with METAVIR fibrosis scores from F0 to F2 ranged from 46.7% to 100%. Because patients with METAVIR fibrosis score greater than F2 are more difficult to treat, this may compromise the generalizability of the results to patients with higher METAVIR fibrosis scores. In addition, results were grouped into F0-F2 and not differentiated between each fibrosis stage.

The dose of EBR/GZR + RBV was used in the C-SALVAGE trial, which included patients with prior experience to DAA; however, this dose was not consistent with Canadian recommendations, and hence the true efficacy of the recommended dose in this patient population is still unknown. The Health Canada recommendation for patients with prior experience with PIs plus PR is EBR/GZR for 12 weeks in patients with genotype 1 who had prior relapse when treated with PIs plus PR, EBR/GZR for 12 weeks in patients with genotype 1b who had on-treatment virologic failures when treated with PIs plus PR, and EBR/GZR + RBV for 16 weeks in patients with genotype 1a who had on-treatment virologic failures when treated with PIs plus PR.

Data were not available from all sites and patients for CLDQ-HCV, as only patients at sites in the US, whose native language was either English or Spanish, were eligible to complete CLDQ-HCV. This may compromise the generalizability of the results of CLDQ-HCV.

## 3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 6). See APPENDIX 4 for detailed efficacy data.

### 3.6.1 Sustained Virologic Response

In the C-EDGE Treatment-Naive study, the SVR12 rate was 95% (95% CI, 92% to 97%) in the treatment-naive genotype 1, 4, or 6 CHC patients who received EBR/GZR for 12 weeks. The lower bound of the 95% CI (92%) exceeded the 73% historical control rate for simeprevir plus PR that was specified as the primary objective (Figure 6). These findings were consistent in key subgroup analyses (by genotype and cirrhosis); SVR12 rates remained high (> 91%) regardless of genotype (1a, 1b, or 4), the presence of cirrhosis, or baseline HCV RNA (Table 14).

In the C-EDGE Coinfection study, the SVR12 rate was 95% (95% CI, 91% to 98%) in the treatment-naive genotype 1, 4, or 6 CHC patients who are coinfected with HIV and received EBR/GZR for 12 weeks. The lower bound of the 95% CI (91%) exceeded the 70% historical control rate for sofosbuvir plus RBV that was specified as the primary objective (Figure 6). These findings were consistent in key subgroup analyses (by genotype and cirrhosis); SVR12 rates remained high (> 91%) regardless of genotype (1a, 1b, or 4), the presence of cirrhosis, antiretroviral therapy with nucleoside reverse transcriptase inhibitors (NRTI) backbone, antiretroviral therapy with third agent in antiretroviral regimen, or baseline HCV RNA (Table 14).

In the C-SURFER study, the SVR12 rate using the mFAS was 99% (95% CI, 95% to 100%) in the treatment-naive or treatment-experienced genotype 1 CHC patients who have CKD and received EBR/GZR for 12 weeks. The lower bound of the 95% CI (95%) exceeded the 45% reference SVR rate that was specified as the primary objective (Table 14). Using the FAS, the SVR rate was 94% (95% CI, 89% to 98%). These findings were consistent in key subgroup analyses, where SVR12 rates remained high (> 95%) regardless of genotype (1a or 1b), the presence of cirrhosis, baseline HCV RNA, prior treatment experience (naive versus experienced), dialysis status at baseline, or CKD stage at baseline (Table 14).

In the C-EDGE Treatment-Experienced study, the SVR12 rates were 92% (95% CI, 86% to 97%), and 97% (95% CI, 92% to 99%) in the treatment-experienced genotype 1, 4, or 6 CHC patients who received EBR/GZR for 12 weeks and EBR/GZR + RBV for 16 weeks, respectively. The lower bound of the 95% CI (86%, and 92%) exceeded the 58% historical control rate for simeprevir plus PR that was specified as the primary objective (Figure 6). SVR rate in patients with genotype 1b who received EBR/GZR for 12 weeks was 100%, while that in patients with genotype 1a in patients who received EBR/GZR + RBV for 16 weeks was 94.8%. SVR rate in patients with genotype 4 who received EBR/GZR for 12 weeks was 77.8%, while that in patients with genotype 4 in patients who received EBR/GZR + RBV for 16 weeks was 100% (Table 14). The findings were consistent in key subgroup analyses, where SVR12 rates remained high (> 81%) regardless of the presence of cirrhosis, HIV coinfection, prior treatment experience, or baseline HCV RNA (Table 14).

In the C-WORTHY trial, the SVR12 rates were 100% in treatment-naive non-cirrhotic patients with genotype 1b, 96.8% in treatment-naive non-cirrhotic patients with genotype 1a, 86.7% in treatment-naive non-cirrhotic patients coinfected with HIV with genotype 1, 96.6% in treatment-naive cirrhotic patients with genotype 1, and 90.9% in treatment-experienced null responder patients with genotype 1b who received EBR/GZR for 12 weeks; and it was 93.5% in treatment-naive non-cirrhotic patients with genotype 1b who received EBR/GZR for eight weeks (Figure 6, and Table 14).

In the C-SALVAGE study, the SVR12 rate was 96% (95% CI, 89% to 99%) in patients with chronic HCV genotype 1 infection who failed a prior approved DAA regimen of boceprevir, telaprevir, simeprevir, or sofosbuvir taken concomitantly with PR who received EBR/GZR + RBV for 12 weeks (Figure 6). These findings were consistent in key subgroup analyses, where SVR12 rates remained high (> 87%) regardless of genotype (1a or 1b), the presence of cirrhosis, baseline HCV RNA, prior treatment experience, or prior DAA regimen received (Table 14).

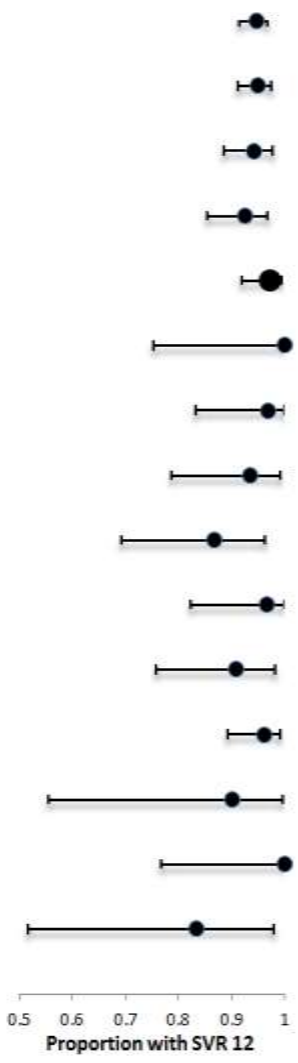
In the C-SCAPE study, the SVR12 rate was 90% (95% CI, 56% to 100%) in treatment-naive patients with chronic HCV genotype 4 infection who received EBR/GZR for 12 weeks. However, only 10 patients were included in this analysis (Figure 6).

In the C-SWIFT study, the SVR12 rate was 100% (95% CI, 77% to 100%) in treatment-naive non-cirrhotic patients with genotype 3 who received EBR/GZR plus SOF for 12 weeks, and it was 83.3% (95% CI, 52% to 98%) in treatment-naive cirrhotic patients with genotype 3 who received EBR/GZR plus SOF for 12 weeks (Figure 6).

Table 11 presents SVR rates by genotype subtype.

**FIGURE 6: PROPORTION OF PATIENTS WHO ACHIEVED SVR12**

| Study | Population | Treatment | N | % SVR12 (95% CI) |
|---|---|---|---|---|
| C-EDGE Treatment-Naive | Naïve with GT 1, 4, or 6 | GZR/EBR for 12 weeks | 316 | 95% (92% to 97%) |
| C-EDGE Co-infection | Naïve with GT 1, 4, or 6 co-infected with HIV | GZR/EBR for 12 weeks | 218 | 95% (91% to 98%) |
| C-SURFER | Naïve or experienced with GT 1 who has CKD | GZR/EBR for 12 weeks | 122 | 94% (89% to 98%) |
| C-EDGE Treatment-Experienced | Experienced with GT 1, 4, or 6 | GZR/EBR for 12 weeks | 105 | 92% (86% to 97%) |
| | Experienced with GT 1, 4, or 6 | GZR/EBR + RBV for 16 weeks | 106 | 97% (92% to 99%) |
| C-WORTHY | Naïve non-cirrhotic GT1b | GZR/EBR for 12 weeks | 13 | 100% (75% to 100%) |
| | Naïve non-cirrhotic GT1a | GZR/EBR for 12 weeks | 31 | 97% (83% to 100%) |
| | Naïve non-cirrhotic GT1b | GZR/EBR for 8 weeks | 31 | 94% (79% to 99%) |
| | Naïve HIV co-infected non-cirrhotic GT1 | GZR/EBR for 12 weeks | 30 | 87% (69% to 96%) |
| | Naïve cirrhotic GT1 | GZR/EBR for 12 weeks | 29 | 97% (82% to 100%) |
| | Experienced null responder GT1 | GZR/EBR for 12 weeks | 33 | 91% (76% to 98%) |
| C-SALVAGE | Experienced with DAA (BOC, TEL, SIM, or SOF) | GZR/EBR + RBV for 12 weeks | 79 | 96% (89% to 99%) |
| C-SCAPE | Naïve GT4 | GZR/EBR for 12 weeks | 10 | 90% (56% to 100%) |
| C-SWIFT | Naïve non-cirrhotic GT3 | GZR/EBR plus SOF for 12 weeks | 14 | 100% (77% to 100%) |
| | Naïve cirrhotic GT3 | GZR/EBR plus SOF for 12 weeks | 12 | 83% (52% to 98%) |




BOC = boceprevir; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; TEL = telaprevir.
Note: Results presented are from the full analysis set population.
Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection;[17] C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE.[20]

**TABLE 11: SUMMARY OF SUSTAINED VIROLOGIC RESPONSE BY GENOTYPE SUBTYPE**

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** | **EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14)** | **EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12)** |
| **SVR12 (full analysis set)** | | | | | | | | | | |
| N (%) [95% CI] | 299 (94.6) [91.5 to 96.8] | NR | 207 (95.0) [91.2 to 97.5][a] | 115/122 (94.3) [88.5 to 97.7] | | NR | 97 (92.4) [85.5 to 96.7] | 103 (97.2) [92.0 to 99.4] | 14(100.0) [76.8 to 100] | 10 (83.3) [51.6 to 97.9] |
| **SVR12 by genotype (full analysis set)[b]** | | | | | | | | | | |
| GT 1a, n/N (%) | 144/157 (91.7) | NR | 136/144 (94.4)[a] | 61/61 (100)[a] | | NR | 55/61 (90.2) | 55/58 (94.8) | NA | NA |
| GT 1b, n/N (%) | 129/131 (98.5) | | 42/44 (95.5) | 54/55 (98.2)[a] | | | 34/34 (100) | 36/36 (100) | NA | NA |
| GT 1 other | NA | | 1/1 (100) | NR | | | 1/1 (100) | 2/2 (100) | NA | NA |
| GT 3, n/N (%) | NA | | NA | NA | | NA | NA | NA | 14/14 (100) | 10/12 (83.3) |
| GT 4, n/N (%) | 18/18 (100) | | 27/28 (96.4) | NA | NA | NA | 7/9 (77.8) | 8/8 (100) | NA | NA |

EBR = elbasvir; GT = genotype; GZR = grazoprevir; ITT = intention-to-treat; NA = not applicable; NR = not reported; PBO = placebo; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

[a] In the article by Rockstroh et al.,[34] it was reported that 210 (96.3%) out of the 218 patients achieved SVR12, with a 95% CI of 92.9% to 98.4%, while the number of patients with GT 1a who achieved SVR12 was 139 (96.5%) out of 144.

[b] GT 6 results are not reported because this use is not an approved indicaiton.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 11: SUMMARY OF SUSTAINED VIROLOGIC RESPONSE BY GENOTYPE SUBTYPE (CONT'D)**

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT1b: EBR/GZR for 12 Weeks (n = 13)** | **TN NC GT1a: EBR/GZR for 12 Weeks (n = 31)** | **TN NC GT1b: EBR/GZR for 8 Weeks (n = 31)** | **TN HIV NC GT1: BR/GZR for 12 Weeks (n = 30)** | **TN C GT1: EBR/GZR for 12 Weeks (n = 29)** | **Null responder GT1: EBR/GZR for 12 Weeks (n = 33)** | **EBR/GZR+ RBV for 12 Weeks (n = 79)** | **EBR/GZR for 12 Weeks (n = 19)** |
| **SVR12 (full analysis set)** | | | | | | | | |
| N (%) [95% CI] | 13 (100.0) [75.3 to 100.0] | 30 (96.8) [83.3 to 99.9] | 29 (93.5) [78.6 to 99.2] | 26 (86.7) [69.3 to 96.2] | 28 (96.6) [82.2 to 99.9] | 30 (90.9) [75.7 to 98.1] | 76 (96.2) [89.3 to 99.2] | 9/10 (90.0) [55.5 to 99.7][a] |
| **SVR12 by genotype (full analysis set)** | | | | | | | | |
| GT 1a, n/N (%) | NA | 29/30 (96.7) | NA | 19/22 (86.4) | 19/20 (95.0) | 20/22 (90.9) | 28/30 (93.3) | NA |
| GT 1b, n/N (%) | 13/13 (100.0) | 1/1 (100.0) | 29/31 (93.5) | 7/8 (87.5) | 7/7 (100) | 10/11 (90.9) | 48/49 (98.0) | NA |
| GT 1 other | NA | NA | NA | NA | 2/2 (100) | NA | NA | NA |
| GT 4, n/N (%) | NA | NA | NA | NA | NA | NA | NA | 9/10 (90.0) |

C = cirrhotic; EBR = elbasvir; GT = genotype; GZR = grazoprevir; HIV = human immunodeficiency virus; NA = not applicable; NC = non-cirrhotic; RBV = ribavirin; SVR12 = sustained virologic response 12 weeks after cessation of study medications; TN = treatment-naive.

[a] Only genotype 4 patients included in this cell.

Source: Buti et al.;[39] Clinical Study Reports: C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE.[20]

### 3.6.2 Response by Resistance-Associated Variants

Subgroup analyses in the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, C-EDGE Treatment-Experienced, and C-SALVAGE trials included signature NS5A RAVs at baseline. It was found that in genotype 1–infected patients who had no baseline NS5A RAVs, SVR12 was achieved in more than 96% of treatment-naive and treatment-experienced patients who received either EBR/GZR for 12 weeks, EBR/GZR + RBV for 16 weeks, or EBR/GZR + RBV for 12 weeks.

Similarly, high efficacy was observed among patients in whom NS5A RAVs associated with a five-fold or less reduction in EBR susceptibility were detected at baseline and in patients with genotype 1b regardless of presence or absence of NS5A RAVs. However, the presence of NS5A RAVs associated with a greater than five-fold decrease in potency to EBR in patients with genotype 1a resulted in reduced efficacy (2/9 [22.2%] in the C-EDGE Treatment-Naive trial, 3/4 [75.0%] in the C-EDGE Coinfection trial, and 6/6 [100%] in the C-SURFER trial) in treatment-naive patients who received EBR/GZR for 12 weeks. Efficacy was also reduced in other trials (2/6 [33.3%] in the C-EDGE Treatment-Experienced trial in treatment-experienced patients who received EBR/GZR for 12 weeks, and 0/1 [0%] in the C-SALVAGE trial in treatment-experienced patients who received EBR/GZR + RBV for 12 weeks; whereas it was 4/4 [100.0%] in the C-EDGE Treatment-Experienced trial in treatment-experienced patients who received EBR/GZR + RBV for 16 weeks) as detailed in Table 12.

There was no evidence that NS3 RAVs had an effect on SVR rate.

**TABLE 12: SUSTAINED VIROLOGIC RESPONSE BY SIGNATURE NS5A RESISTANCE-ASSOCIATED VARIANTS AT BASELINE**

| | Treatment-Naive Patients | | Mixed Experience | | Treatment-Experienced Patients | | |
|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | C-EDGE Coinfection | C-SURFER | | C-EDGE Treatment-Experienced | | C-SALVAGE |
| | EBR/GZR for 12 Weeks (n = 316) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11) | EBR/GZR for 12 Weeks (n = 111) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) | EBR/GZR + RBV for 12 Weeks (n = 79) |
| **SVR12 (full analysis set)** | | | | | | | |
| n/N (%) | 299/316 (94.6) | 207/218 (95.0) | 115/122 (94.3) | | 97/105 (92.4) | 103/106 (97.2) | 76/79 (96.2) |
| **Signature NS5A RAVs at baseline, n/N (%)** | | | | | | | |
| **Genotype 1a** | | | | | | | |
| None detected by population sequencing | 133/135 (98.5) | 127/130 (97.7) | 54/54 (100)[a] | | 49/50 (98.0) | 49/49 (100.0) | 25/26 (96.1%) |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | 9/10 (90.0) | 5/6 (83.3) | 1/1 (100)[a] | | 4/4 (100.0) | 2/2 (100.0) | 3/3 (100%) |
| NS5A RAVs with > 5x elevation in EBR $EC_{50}$ | 2/9 (22.2) | 3/4 (75.0) | 6/6 (100)[a] | | 2/6 (33.3) | 4/4 (100.0) | 0/1 (0.0%) |
| **Genotype 1b** | | | | | | | |
| None detected by population sequencing | 112/112 (100) | 37/38 (97.4) | 44/44 (100)[a] | | 32/32 (100.0) | 33/33 (100.0) | 45/45 (100.0%) |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | 1/1 (100) | 0/0 (NA) | 0/0 (NA) | | 0/0 (NA) | 0/0 (NA) | 0/0 (NA) |
| NS5A RAVs with > 5x elevation in EBR $EC_{50}$ | 16/17 (94.1) | 5/5 (100) | 9/10 (90)[a] | | 2/2 (100.0) | 3/3 (100.0) | 3/4 (75.0%) |
| **Genotype 4** | | | | | | | |
| None detected by population sequencing | 9/9 (100) | 16/17 (94.1) | NA | | 6/7 (85.7) | 4/4 (100) | NA |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | 9/9 (100) | 11/11 (100) | NA | | 1/1 (100) | 4/4 (100) | NA |
| NS5A RAVs with >5x elevation in EBR $EC_{50}$ | | | NA | | | | NA |

$EC_{50}$ = effective concentration necessary to inhibit a replicon; EBR = elbasvir; FAS = full analysis set; GT = genotype; GZR = grazoprevir; HCV = hepatitis C virus; mFAS = modified full analysis set; NA = not applicable; NS5A = nonstructural protein 5A; PK = pharmacokinetic; RAV = resistance-associated variant; RBV = ribavirin; SVR12 = sustained virologic response 12 weeks after cessation of study medications.

[a] The mFAS population is a subset of the FAS population with patients, with patients excluded for the following reasons: failure to receive at least one dose of active study treatment, missing data due to death with reasons unrelated to study drug or reasons other than liver disease, and missing data due to study discontinuation with reasons unrelated to progression of liver disease, study drug and their responses to the HCV treatment.

### 3.6.3 Relapse and On-Treatment Failure

In the C-EDGE Treatment-Naive trial, 9/157 (5.7%) of patients with genotype 1a, 1/131 (0.8%) of patients with genotype 1b, and 0% of patients with genotype 4 had relapse, and 1/157 (0.6%) of patients with genotype 1a had virologic breakthrough. Among the 10 genotype 1a–infected patients who experienced virologic failure, 9 (90%) had treatment-emergent NS5A RAVs at failure. Seven of the nine patients with treatment-emergent RAVs also had baseline RAVs that cause a greater than five-fold decrease in EBR potency. In the single genotype 1b–infected patient who experienced virologic failure, a treatment-emergent NS5A RAV was detected at failure.

In the C-EDGE Coinfection trial, 5/144 (3.5%) of patients with genotype 1a, 1/44 (2.3%) of patients with genotype 1b, and 1/28 (3.6%) of patients with genotype 4 had relapse. None of the patients had virologic breakthrough. All four relapsed patients were assessed for treatment-emergent mutations: two patients had NS3 and three had NS5A.

In the C-SURFER trial, 1/55 (1.8%) of patients with genotype 1b had relapse, and none of the patients had virologic breakthrough. The relapsed patient had NS5A.

In the C-EDGE Treatment-Experienced trial, in patients who received EBR/GZR for 12 weeks, 5/61 (8.2%) of patients with genotype 1a and 1/9 (11.1%) of patients with genotype 4 had relapse; none of the patients had virologic breakthrough. In patients who received EBR/GZR + RBV for 16 weeks, none of the patients had relapse or virologic breakthrough.

In the C-SALVAGE trial, 2/30 (6.7%) of patients with genotype 1a, and 1/49 (2.0%) of patients with genotype 1b had relapse (Table 14).

In the C-SWIFT study, there was 1/12 (8.3%) relapse in treatment-naive cirrhotic patients with genotype 3 (Table 14).

### 3.6.4 Health-Related Quality of Life

HRQoL data were measured using the SF-36, EQ VAS scores, and CLDQ-HCV scores, in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials. HRQoL data were measured using the SF-36 scores in the C-SURFER trial.

#### a) SF-36

In the C-EDGE Treatment-Naive trial, the EBR/GZR group had statistically significant improvements over baseline in the vitality domain (mean change from baseline 2.52 [95% CI, 0.18 to 4.87]) of the SF-36 and the MCS (mean change from baseline 1.28 [95% CI, 0.25 to 2.32] at week 12, a non-statistically significant increase in the general health (1.62 [95% CI, –0.20 to 3.44]), role physical (1.30 [95% CI, –1.23 to 3.84]), and role emotional (2.36 [95% CI, –0.24 to 4.96]) domains, and a non-statistically significant decrease in the PCS (–0.61 [95% CI, –2.01 to 0.79]) over the same time period. At week 12, the mean difference in change in the MCS between the EBR/GZR and placebo groups was 2.33 (95% CI, 0.28 to 4.37), in favour of EBR/GZR; on the other hand, there was no statistical significance between EBR/GZR and placebo groups in the vitality, general health, role physical, and role emotional domains of the SF-36 and the PCS. At follow-up week 4, the mean difference in change in the general health and role physical domains between the EBR/GZR and placebo groups was 4.94 (95% CI, 1.30 to 8.59), and 4.97 (95% CI, 0.17 to 9.77), respectively, in favour of EBR/GZR. There was no statistical significance between the EBR/GZR and placebo groups in vitality and role emotional domains of the SF-36 and the MCS and PCS (Table 15). In the C-EDGE Coinfection trial, at week 12, mean improvement from baseline was seen in vitality (5.07

[95% CI, 2.48 to 7.67]), general health (5.04 [95% CI, 2.91 to 7.18]) domains and the MCS (1.46 [95% CI, 0.16 to 2.76]), while no statistically significant improvement was shown in the role physical and role emotional domains and the PCS. At follow-up week 12, only the vitality domain had mean improvement from baseline of 3.45 (95% CI, 0.28 to 6.63); none of the other domains showed statistically significant improvement at follow-up week 12 (Table 15).

In the C-SURFER trial, the change from baseline in vitality, general health, role physical, and role emotional domains, MCS, and PCS at treatment week 12 for the GZR + EBR and the placebo groups were not statistically significant; in addition, the mean changes from baseline in HRQoL scores at treatment week 12 did not differ between the GZR + EBR and placebo groups for any of these domains with a between-group difference at week 12 of 3.03 (95% CI, –2.29 to 8.35) for vitality, 3.55 (95% CI, –0.88 to 7.98) for general health, 4.04 (95% CI, –3.24 to 11.31) for role physical, –4.93 (95% CI, -12.31 to 2.45) for role emotional, -0.69 (95% CI, -3.21 to 1.82) for MCS and 1.71 (95% CI, -0.51 to 3.93) for PCS (Table 15).

In the C-EDGE Treatment-Experienced trial, in the EBR/GZR for 12 weeks group, statistically significant improvements from baseline scores occurred in vitality and general health domains during treatment at week 12, with no statistically significant improvement reported for role physical and role emotional domains, MCS, and PCS at treatment week 12. In contrast, statistically significant declines from baseline scores were observed in vitality, role physical, and role emotional domains, PCS, and MCS during treatment with EBR/GZR + RBV for 16 weeks (Table 15).

**b) EQ-5D VAS Scores**

In the C-EDGE Treatment-Naive trial, the EQ-5D VAS improved from baseline to week 12 in the EBR/GZR group, but the difference in mean change from baseline to week 12 was not statistically different from placebo: 2.25 (95% CI, –0.65 to 5.55). At follow-up week 4, the difference in mean change from baseline in EQ-5D VAS score was greater in the EBR/GZR group than in the placebo group (treatment difference: 5.42 [95% CI, 1.87 to 8.97]) (Table 16). While the improvement from baseline in EQ-5D VAS at follow-up week 12 for the EBR/GZR group was statistically significant, 2.83 (95% CI, 1.12 to 4.55), no statistical comparison was made between the EBR/GZR and placebo groups for the difference in mean change.

In the C-EDGE Coinfection trial, EQ-5D VAS improved while on-treatment at treatment week 12 (3.74 [95% CI, 1.70 to 5.78]) and through follow-up week 12 (2.77 [95% CI, 0.41 to 5.14]) (Table 16

Table 16).

In the C-EDGE Treatment-Experienced trial, there were no statistical differences in the change from baseline in the EBR/GZR and EBR/GZR + RBV group during treatment. However, at follow-up week 12, there was a statistically significant improvement in EQ-5D VAS score for both the EBR/GZR 12 weeks (4.60 [95% CI, 1.53 to 7.68]) and EBR/GZR + RBV 16 weeks arms (4.65 [95% CI, 1.95 to 7.35) (Table 16

Table 16).

**c) CLDQ-HCV Scores**

Only at sites in the US, patients whose native language was either English or Spanish were eligible to complete CLDQ-HCV; hence, there were many missing data for this outcome.

In the C-EDGE Treatment-Naive trial, for both the EBR/GZR and placebo groups, Overall CLDQ-HCV mean scores improved from baseline at treatment week 12, and at follow-up week 4. The improvement in the EBR/GZR group was also statistically significant at follow-up week 12. The differences in the mean

change from baseline between the EBR/GZR and placebo groups were not statistically significant at week 12 (0.02 [95% CI, 0–23 to 0.26]) and at follow-up week 4 (0.12 [95% CI, –0.13 to 0.37]) (Table 18Table 18).

In the C-EDGE Coinfection trial, there were statistically significant improvements from baseline for overall score at treatment week 12 (0.63 [95% CI, 0.39 to 0.87]), and at follow-up week 12 (0.69 [95% CI, 0.41 to 0.98]) (Table 18Table 18).

In the C-EDGE Treatment-Experienced trial, in the EBR/GZR for 12 weeks arm, mean improvements from baseline were seen in the Overall CLDQ-HCV score at follow-up week 12 (0.47 [95% CI, 0.25 to 0.68]), but not at treatment week 12 (0.24 [95% CI, –0.01 to 0.48]). In the EBR/GZR + RBV for 16 weeks arm, changes from baseline in Overall CLDQ-HCV were not statistically significant at treatment week 12 (–0.12 [95% CI, –0.40 to 0.15]), but were statistically significantly improved at follow-up week 12 (0.34 [95% CI, 0.07 to 0.61]) (Table 18Table 18).

### 3.6.5 Other Patient-Reported Outcomes

The symptom scale FACIT-F and WPAI (an instrument used to measure the impact of a disease on work and daily activities) were used in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials.

#### a) FACIT-F Scale

In the C-EDGE Treatment-Naive trial, no treatment differences in mean change from baseline in fatigue scores between EBR/GZR and placebo were shown at treatment week 12 (0.19 [95% CI, –1.86 to 2.24]) and follow-up week 4 (1.54 [95% CI, –0.37 to 3.44]). Overall, mean scores improved from baseline, indicating less fatigue, at follow-up week 4 (1.73 [95% CI, 0.75 to 2.71]) and follow-up week 12 (1.74 [95% CI, 0.78 to 2.70]) in the EBR/GZR group (Table 17).

In the C-EDGE Coinfection trial, overall FACIT-F scores improved through treatment week 12, with patients indicating less fatigue at treatment week 12 (2.31 [95% CI, 1.02 to 3.59]) and follow-up week 12 (1.69 [95% CI, 0.11 to 3.27]) than at baseline (Table 17Table 17).

In the C-EDGE Treatment-Experienced trial, in the EBR/GZR for 12 weeks arm, there was a non-statistically significant improvement in fatigue scores at weeks 12 (1.42 [95% CI, –0.49 to 3.34]). The improvement over baseline in fatigue scores was statistically significant at follow-up week 12 (3.60 [95% CI, 2.04 to 5.17]). In the EBR/GZR + RBV for 16 weeks arm, FACIT-F scores decreased, indicating worsening fatigue, over time at treatment week 12 (–4.07 [95% CI, –5.99 to –2.15]) but did not differ statistically from baseline by follow-up week 12 (0.87 [95% CI, –0.57 to 2.30) (Table 17).

#### b) WPAI

In the C-EDGE Treatment-Naive trial, among patients who were employed, no treatment differences in mean change from baseline in overall impairment between EBR/GZR and placebo were shown at treatment week 12 (–3.56 [95% CI, –8.92 to 1.81]) and follow-up week 4 (–2.16 [95% CI, –7.22 to 2.91]). Overall, mean scores declined from baseline, indicating less impairment while working due to hepatitis C than at baseline, at follow-up week 12 (–2.74 [95% CI, –4.96 to -0.51]) in the EBR/GZR group. There were no treatment differences in mean change from baseline in activity impairment due to hepatitis C between the EBR/GZR and placebo groups at treatment week 12 (–0.34 [95% CI, –4.80 to 4.13]) and follow-up week 4 (–3.27 [95% CI, –8.02 to 1.47]). Overall, mean scores declined from baseline, indicating

less activity impairment due to hepatitis C than at baseline, at follow-up week 4 (–4.34 [95% CI, –6.82 to –1.87]) and at follow-up week 12 (–6.36 [95% CI, –8.78 to –3.94]) (Table 19Table 19).

In the C-EDGE Coinfection trial, among patients who were employed, there was a non-statistically significant decrease from baseline in overall impairment in the EBR/GZR treatment group at treatment week 12 (–1.14 [95% CI, –5.10 to 2.83]) and at follow-up week 12 (–3.74 [95% CI, –8.77 to 1.28]). Activity impairment due to hepatitis C had decreased, indicating less impairment over time at treatment week 12 (–6.47 [95% CI, –10.19 to –2.74]), and follow-up week 12 (–9.71 [95% CI, –13.88 to –5.54]) (Table 19Table 19).

In the C-EDGE Treatment-Experienced trial, among patients who were employed, in the EBR/GZR for 12 weeks arm, there was a non-statistically significant decrease from baseline in overall impairment due to CHC at treatment week 12 (–1.14 [95% CI, –4.60 to 2.32]); however, there was statistically significantly less impairment while working due to CHC than at baseline, at follow-up week 12 (–6.50 [95% CI, –10.97 to –2.03]). Similarly, there was a non-statistically significant decrease from baseline in activity impairment due to CHC at treatment week 12 (–2.73 [95% CI, –7.12 to 1.67]); however, there was statistically significantly less activity impairment due to CHC than at baseline, at follow-up week 12 (–6.56 [95% CI, –11.26 to –1.86]). Among patients who were employed, in the EBR/GZR + RBV for 16 weeks arm, there was a statistically significant increase from baseline in overall impairment due to CHC at treatment week 12 (11.25 [95% CI, 4.35 to 18.15]), but there was a non-statistically significant decline from baseline in overall impairment while working due to CHC than at baseline, at follow-up week 12 (–1.46 [95% CI, –7.77 to 4.85]). Similarly, there was a statistically significant increase from baseline in activity impairment due to CHC at treatment week 12 (10.98 [95% CI, 5.54 to 16.42]); however, there was a non-statistically significant decline from baseline in activity impairment due to CHC than at baseline, at follow-up week 12 (–1.21 [95% CI, –6.18 to 3.77]) (Table 19Table 19).

## 3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Table 20 for detailed harms data.

### 3.7.1 Adverse Events

The proportion of patients who reported adverse events ranged from 53.3% to 91.7% while on EBR/GZR for 12 weeks, 54.8% among those who received EBR/GZR for eight weeks, 79.7% among those who received EBR/GZR + RBV for 12 weeks, 89.6% among those who received EBR/GZR + RBV for 16 weeks, and ranged from 21.4% to 33.3% among those who received EBR/GZR plus SOF for 12 weeks. The proportion of placebo-treated patients who reported adverse events ranged from 68.6% to 84.1% (Table 13).

### 3.7.2 Serious Adverse Events

The rates of serious adverse events ranged from 0% to 3.8% while on EBR/GZR for 12 weeks, 0% among those who received EBR/GZR for eight weeks, 5.1% among those who received EBR/GZR + RBV for 12 weeks, 3.8% among those who received EBR/GZR + RBV for 16 weeks, 0% to 14.4% in patients who received EBR/GZR for 12 weeks and have CKD, and ranged from 0% to 8.3% among those who received EBR/GZR plus SOF for 12 weeks. In those who received placebo, rates of SAE were 2.9% in the C-EDGE Treatment-Naive trial and 16.8% for patients with CKD (Table 13).

### 3.7.3 Withdrawals Due to Adverse Events

Few patients discontinued therapy due to adverse events. Where the rates of discontinued therapy due to adverse events ranged from 0% to 1% while on EBR/GZR for 12 weeks, 0% among those who received EBR/GZR for eight weeks, 1.3% among those who received EBR/GZR + RBV for 12 weeks, 4.7% among those who received EBR/GZR + RBV for 16 weeks, 0% in patients who received EBR/GZR for 12 weeks and have CKD, and 0% among those who received EBR/GZR plus SOF for 12 weeks. For those who received placebo, rates of discontinued therapy due to adverse events were 1% in the C-EDGE Treatment-Naive trial and 4.4% for patients with CKD (Table 13).

### 3.7.4 Mortality

Two deaths were reported in the C-EDGE Treatment-Naive trial in EBR/GZR for the 12-weeks arm; both deaths were considered unrelated to study medication. For one death, the cause was considered to be due to an incarcerated hiatal hernia, and the other death was presumed to be due to an arrhythmia from autopsy-documented coronary disease. In the C-SURFER trial, there were five deaths (2.1%) that occurred during treatment and follow-up. One patient was in the EBR/GZR for 12 weeks treatment group and four patients were in the placebo group. No deaths were considered related to study medication. No further deaths were reported in any other trial.

### 3.7.5 Notable Harms

Patients treated with EBR/GZR reported the occurrence of diarrhea (3.4% to 12.9%), nausea (3.3% to 16.7%), fatigue (6.7% to 33.3%), headache (6.7% to 41.7%), and pruritus (0% to 7.6%), while patients treated with EBR/GZR + RBV reported the occurrence of diarrhea (0% to 8.5%), nausea (11.4% to 17.0%), fatigue (27.8% to 30.2%), headache (19%), and pruritus (3.8% to 10.4%), and those on EBR/GZR + SOF reported diarrhea (0% to 8.3%), nausea (7.1% to 8.3%), fatigue (0% to 8.3%), headache (0% to 8.3%), and pruritus (0% to 7.1%).

Anemia, defined as a decline in hemoglobin to < 100 g/L, was reported in 0% to 3.2% of patients who received EBR/GZR, while it was 10.1% in patients who received EBR/GZR + RBV for 12 weeks, 20.7% in patients who received EBR/GZR + RBV for 16 weeks, and 0% in patients who received EBR/GZR + SOF. In patients who have CKD, it ranged from 28.8% to 36.4% in patients who received EBR/GZR and was 21.2% in patients who received placebo. Of note in the C-SURFER trial, Hgb values in the EBR/GZR group (mean 120 g/L, median 119 g/L, range 82 to 168 g/L) were comparable to those in the placebo group (mean 118 g/L, median 118 g/L, range 88 to 168 g/L) at baseline. Anemia is more prevalent in general in the CKD population, and treatment with erythropoietin-stimulating agents is common. The overall use of erythropoietin-stimulating agents in the EBR/GZR group was 24%, lower than the reported use in the placebo arm (30%).

In the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, C-EDGE Treatment-Experienced, and C-WORTHY trials, alanine aminotransferase (ALT) > 5x ULN (upper limit of normal) was reported in a few patients in the trials, ranging from 0% to 2.3% in patients who received EBR/GZR, and 1.8% to 8.6% in patients who received placebo, but none of the patients had bilirubin > 5x ULN. In the C-SALVAGE trial, none of the patients had ALT > 5x ULN, but one patient (1.3%) had bilirubin > 5x ULN. In the C-SCAPE trial, two patients (10.6%) had ALT > 5x ULN, but none of the patients had bilirubin > 5x ULN.

**TABLE 13: HARMS**

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks | PBO 12 Weeks | EBR/GZR for 12 Weeks | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) | EBR/GZR for 12 Weeks | PBO 12 Weeks | EBR/GZR for 12 Weeks | EBR/GZR + RBV for 16 Weeks | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) |
| N | 316 | 105 | 218 | 11 | 111 | 113 | 105 | 106 | 14 | 12 |
| Any AE, n (%) | 213 (67.4) | 72 (68.6) | 161 (73.9) | 9 (81.8) | 84 (75.7) | 95 (84.1) | 74 (70.5) | 95 (89.6) | 3 (21.4) | 4 (33.3) |
| SAE, n (%) | 9 (2.8) | 3 (2.9) | 2 (0.9) | 0 | 16 (14.4) | 19 (16.8) | 4 (3.8) | 4 (3.8) | 0 | 1 (8.3) |
| Death, n (%) | 2 (0.6) | 0 | 0 | 0 | 1 (0.9) | 3 (2.7) | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug, n (%) | 3 (0.9) | 1 (1.0) | 0 | 0 | 0 | 5 (4.4) | 1 (1.0) | 5 (4.7) | 0 | 0 |
| **Notable harms** | | | | | | | | | | |
| Nausea | 28 (8.9) | 8 (7.6) | 20 (9.2) | 1 (9.1) | 17 (15.3) | 18 (15.9) | 9 (8.6) | 18 (17.0) | 1 (7.1) | 1 (8.3) |
| Fatigue | 49 (15.5) | 18 (17.1) | 29 (13.3) | 2 (18.2) | 11 (9.9) | 17 (15.0) | 20 (19.0) | 32 (30.2) | 0 | 1 (8.3) |
| Pruritus | 7 (2.2) | 8 (7.6) | 5 (2.3) | 0 | 4 (3.6) | 11 (9.7) | 1 (1.0) | 11 (10.4) | 1 (7.1) | 0 |
| Headache | 52 (16.5) | 19 (18.1) | 27 (12.4) | 4 (36.4) | 19 (17.1) | 19 (16.8) | 22 (21.0) | 20 (18.9) | 0 | 1 (8.3) |
| ALT elevations | | | | | | | | | | |
| 1.25 to 2.5 ULN | 5 (1.6) | 26 (24.8) | 8 (3.7) | 0 | 3 (2.7) | 25 (22.1) | 3 (2.9) | 3 (2.8) | 0 | 0 |
| 2.6 to 5 ULN | 4 (1.3) | 20 (19.0) | 2 (0.9) | 0 | 1 (0.9) | 3 (2.7) | 0 | 1 (0.9) | 0 | 0 |
| 5.1 to 10 ULN | 1 (0.3) | 9 (8.6) | 3 (1.4) | 0 | 0 | 2 (1.8) | 1 (1.0) | 0 | 0 | 0 |
| > 10 ULN | 3 (0.9) | 0 | 2 (0.9) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1.1 to 2.5 baseline | 9 (2.8) | 58 (55.2) | 11 (5.0) | 0 | 2 (1.8) | 36 (31.9) | 2 (1.9) | 3 (2.8) | 0 | 0 |
| > 2.5 to 5.0 baseline | 2 (0.6) | 2 (1.9) | 0 | 0 | 1 (0.9) | 6 (5.3) | 0 | 0 | 0 | 0 |
| > 5.0 baseline | 3 (0.9) | 0 | 2 (0.9) | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 |
| Bilirubin elevations | | | | | | | | | | |
| 1.1 - 1.5 x ULN | 19 (6.0) | 4 (3.8) | 10 (4.6) | 0 | 1 (0.9) | 2 (1.8) | 8 (7.6) | 27 (25.5) | 0 | 2 (16.7) |
| 1.6 - 2.5 x ULN | 8 (2.5) | 4 (3.8) | 6 (2.8) | 0 | 0 | 2 (1.8) | 1 (1.0) | 20 (18.9) | 0 | 1 (8.3) |
| 2.6 - 5.0 x ULN | 1 (0.3) | 0 | 1 (0.5) | 0 | 0 | 0 | 0 | 9 (8.5) | 0 | 0 |
| > 5.0 x ULN | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks | PBO 12 Weeks | EBR/GZR for 12 Weeks | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) | EBR/GZR for 12 Weeks | PBO 12 Weeks | EBR/GZR for 12 Weeks | EBR/GZR + RBV for 16 Weeks | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) |
| > 2.5 - 5.0 x baseline | 3 (0.9) | 0 | 8 (3.7) | 0 | 1 (0.9) | 3 (2.7) | 1 (1.0) | 35 (33.0) | 0 | 1 (8.3) |
| > 5.0 - 10.0 x baseline | 1 (0.3) | 0 | 1 (0.5) | 0 | 0 | 0 | 0 | 4 (3.8) | 0 | 0 |
| > 10.0 x baseline | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anemia | | | | | | | | | | |
| Hemoglobin (100 to 109 g/L) | 6 (1.9) | 4 (3.8) | 3 (1.4) | 2 (18.2) | 24 (21.6) | 26 (23.0) | 3 (2.9) | 15 (14.2) | 0 | 1 (8.3) |
| Hemoglobin (90 to 99 g/L) | 3 (0.9) | 0 | 0 | 3 (27.3) | 20 (18.0) | 16 (14.2) | 0 | 17 (16.0) | 0 | 0 |
| Hemoglobin (70 to 89 g/L) | 0 | 0 | 0 | 1 (9.1) | 11 (9.9) | 6 (5.3) | 0 | 4 (3.8) | 0 | 0 |
| Hemoglobin (< 70 g/L) | 0 | 0 | 0 | 0 | 1 (0.9) | 2 (1.8) | 0 | 1 (0.9) | 0 | 0 |

AE = adverse event; ALT = alanine aminotransferase; EBR = elbasvir; GZR = grazoprevir; PBO = placebo; PK = pharmacokinetic; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir; ULN = upper limit of normal.
[a] Frequency > 10%.
Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 12: HARMS (CONT'D)**

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | TN NC GT1b: EBR/GZR for 12 Weeks | TN NC GT1a: EBR/GZR for 12 Weeks | TN NC GT1b: EBR/GZR for 8 Weeks | TN HIV NC GT1: EBR/GZR for 12 Weeks | TN C GT1: EBR/GZR for 12 Weeks | Null responder GT1: EBR/GZR for 12 Weeks | EBR/GZR + RBV for 12 Weeks | EBR/GZR for 12 Weeks |
| N | 12 | 31 | 31 | 30 | 29 | 33 | 79 | 19 |
| Any AE, n (%) | 11 (91.7) | 27 (87.1) | 17 (54.8) | 16 (53.3) | 19 (65.5) | 26 (78.8) | 63 (79.7) | 15 (78.9) |
| SAE, n (%) | 0 | 0 | 0 | 1 (3.3) | 2 (6.9) | 1 (3.0) | 4 (5.1) | 0 |
| Death, n (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to discontinuation of study drug, n (%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3) | 1 (5.3) |
| **Notable harms** | | | | | | | | |
| Nausea | 2 (16.7) | 5 (16.1) | 3 (9.7) | 1 (3.3) | 0 | 2 (6.1) | 9 (11.4) | 1 (5.3)0 |

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT1b: EBR/GZR for 12 Weeks** | **TN NC GT1a: EBR/GZR for 12 Weeks** | **TN NC GT1b: EBR/GZR for 8 Weeks** | **TN HIV NC GT1: EBR/GZR for 12 Weeks** | **TN C GT1: EBR/GZR for 12 Weeks** | **Null responder GT1: EBR/GZR for 12 Weeks** | **EBR/GZR + RBV for 12 Weeks** | **EBR/GZR for 12 Weeks** |
| Fatigue | 4 (33.3) | 6 (19.4) | 3 (9.7) | 2 (6.7) | 6 (20.7) | 10 (30.3) | 22 (27.8) | 2 (10.5) |
| Pruritus | 0 | 0 | 0 | 0 | 1 (3.4) | 2 (6.1) | 3 (3.8) | 1 (5.3) |
| Headache | 5 (41.7) | 10 (32.3) | 5 (16.1) | 2 (6.7) | 4 (13.8) | 6 (18.2) | 15 (19.0) | 1 (5.3) |
| ALT elevations | | | | | | | | |
| 1.25 to 2.5 ULN | 2 (16.7) | 0 | 0 | 2 (6.7) | 0 | 0 | 0 | 0 |
| 2.6 to 5 ULN | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5.1 to 10 ULN | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5.3) |
| > 10 ULN | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5.3) |
| 1.1 to 2.5 baseline | 2 (16.7) | 0 | 0 | 2 (6.7) | 0 | 0 | 0 | 1 (5.3) |
| > 2.5 to 5.0 baseline | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| > 5.0 baseline | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5.3) |
| Bilirubin elevations | | | | | | | | |
| 1.1 - 1.5 x ULN | 1 (8.3) | 0 | 1 (3.2) | 2 (6.7) | 2 (6.9) | 1 (3.0) | 20 (25.3) | 0 |
| 1.6 - 2.5 x ULN | 0 | 0 | 1 (3.2) | 1 (3.3) | 1 (3.4) | 2 (6.1) | 18 (22.8) | 0 |
| 2.6 - 5.0 x ULN | 0 | 0 | 0 | 0 | 0 | 0 | 4 (5.1) | 1 (5.3) |
| > 5.0 x ULN | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.3) | 0 |
| > 2.5 - 5.0 x baseline | 0 | 0 | 0 | 2 (6.7) | 0 | 0 | 28 (35.4) | 1 (5.3) |
| > 5.0 - 10.0 x baseline | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.5) | 0 |
| > 10.0 x baseline | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anemia | | | | | | | | |
| Hemoglobin (100 to 109 g/L) | 1 (8.3) | 0 | 1 (3.2) | 1 (3.3) | 0 | 0 | 14 (17.7) | 0 |
| Hemoglobin (90 to 99 g/L) | 0 | 0 | 1 (3.2) | 0 | 0 | 0 | 6 (7.6) | 0 |
| Hemoglobin (70 to 89 g/L) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.5) | 0 |
| Hemoglobin < 70 g/L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

AE = adverse event; ALT = alanine aminotransferase; C = cirrhotic; EBR = elbasvir; GT = genotype; GZR = grazoprevir; HIV = human immunodeficiency virus; NC = non-cirrhotic; RBV = ribavirin; SAE = serious adverse event; TN = treatment-naive; ULN = upper limit of normal.

[a] Frequency > 10%.

Source: Clinical Study Reports: C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE.[20]

# 4. DISCUSSION

## 4.1 Summary of Available Evidence

A total of eight trials were included in this review: three pivotal phase 3 clinical trials (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-EDGE Treatment-Experienced) and three pivotal phase 2 clinical trials (C-SWIFT, C-WORTHY, C-SALVAGE). C-SURFER was a phase 3 clinical trial that was not pivotal but met our inclusion criteria, and C-SCAPE was a phase 2 trial that was considered pivotal by the manufacturer but not Health Canada. Two trials were randomized, double-blinded placebo-controlled trials (C-EDGE Treatment-Naive and C-SURFER); three trials were randomized, parallel-group, open-label trials (C-EDGE Treatment-Experienced, C-SWIFT, and C-WORTHY); and three were open-label non-randomized trials (C-EDGE Coinfection, C-SALVAGE, and C-SCAPE).

The trials enrolled adults with CHC genotypes 1, 4, or 6 (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-EDGE Treatment-Experienced), genotype 1 (C-SURFER, C-SALVAGE), genotypes 1 or 3 (C-SWIFT, C-WORTHY), or genotypes 2, 4, 5, or 6 (C-SCAPE). Four trials enrolled patients who were treatment-naive (C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SWIFT, C-SCAPE); two trials included treatment-experienced patients (C-EDGE Treatment-Experienced, C-SALVAGE); and two trials included treatment-naive and treatment-experienced patients (C-SURFER, C-WORTHY). In the C-EDGE Treatment-Experienced study, the treatment-experienced patients had a prior null, partial response or relapse to PR, while in the C-SALVAGE study, the treatment-experienced patients had prior non-response, breakthrough, or relapse to PR + DAA. In the C-SURFER study, the treatment-experienced patients had prior interferon or prior PR treatment failures (null responders, partial responders, or relapsers). Patients included in the C-EDGE Coinfection study had to be coinfected with HIV, and patients included in the C-SURFER study had to have CKD.

The main outcome in the included trials was the proportion of patients achieving SVR at 12 weeks (SVR12). The main limitation of the included trials was the lack of an active treatment comparator arm consisting of an existing treatment regimen for chronic hepatitis C genotype 1, 3, or 4 infection. The primary outcome in the C-EDGE Treatment-Naive, C-EDGE Coinfection, C-SURFER, and C-EDGE Treatment-Experienced trials was compared versus a historical control (SVR12 rates from trials that evaluated simeprevir plus PR, SOF plus RBV, or PR). These comparisons to a historical control could be biased due to differences in the distribution of potential confounders of effect; in addition, the historical controls used were based on older regimens, which are less efficacious than the currently available interferon-free regimens; in addition, an arbitrary reduction in the historical rate of 5% for the anticipated improvement of safety profile related to an interferon-free regimen was done. Limited data were available in patients with genotype 3 and 4 CHC.

## 4.2 Interpretation of Results

### 4.2.1 Efficacy

The manufacturer is seeking reimbursement for EBR/GZR consistent with the Health Canada indication; i.e., in patients with CHC genotype 1, 3, or 4 infection. In the patient group input received by CDR for this submission, patients' expectations about the drug(s) under review were to cure the infection and provide treatment options for patients who have failed standard therapy, those who have contraindications or cannot tolerate interferon, those coinfected with HIV, those with kidney impairment, those with compensated cirrhosis, and those infected with rare and/or multiple HCV genotypes. (See Appendix 1.)

In treatment-naive patients infected with genotype 1 or 4, the Health Canada–approved regimen of EBR/GZR for 12 weeks was associated with high rates of successful treatment (94.6% of patients achieving SVR12). This rate was higher than (absolute difference ≥ 21.6%) and statistically superior to the historical comparator (simeprevir plus PR) SVR rate. In treatment-naive patients with genotypes 1 or 4, coinfected with HIV, the Health Canada–approved regimen of EBR/GZR for 12 weeks was associated with high rates of successful treatment (95% of patients achieving SVR12). This rate was higher than (absolute difference ≥ 25%) and statistically superior to the historical comparator (SOF plus RBV) SVR rate. In treatment-naive and treatment-experienced patients with genotype 1 who have CKD, the Health Canada–approved regimen of EBR/GZR for 12 weeks was associated with high rates of successful treatment (94.3% of patients achieving SVR12). This rate was higher than (absolute difference ≥ 49.3%) and statistically superior to the historical comparator (PR) SVR rate. In treatment-experienced patients with genotypes 1 or 4, the Health Canada–approved regimens of EBR/GZR for 12 weeks and EBR/GZR plus RBV for 16 weeks were associated with high rates of successful treatment (92.4% and 97.2% of patients achieving SVR12, respectively). This rate was higher than (absolute difference ≥ 34.4%, and 39.2%) and statistically superior to the historical comparator (simeprevir plus PR) SVR rate. It is worth noting that the dose recommended by Health Canada is EBR/GZR + RBV for 16 weeks for patients with genotype 1a and genotype 4 who had prior virologic response, and EBR/GZR for 12 weeks is recommended for patients with genotype 1b regardless of prior treatment response and patients with genotype 1a who are relapsers. However, results in the C-EDGE Treatment-Experienced study were not reported by genotype subtype and prior treatment experience; hence, the exact SVR rate of EBR/GZR for 12 weeks and EBR/GZR + RBV for 16 weeks, especially in patients with genotype 1a, is unknown.

Overall, EBR/GZR for 12 weeks achieved SVR12 rates between 90% and 100% among patients with genotype 1 CHC, and showed similar response rates regardless of the patients' prior treatment history, genotype subtype, presence of CKD, or presence of cirrhosis. EBR/GZR for 12 weeks also achieved SVR12 rates between 87% and 96% among treatment-naive patients with genotype 1 CHC who are coinfected with HIV. EBR/GZR for eight weeks achieved SVR12 rates of 94% among treatment-naive patients with genotype 1b CHC. Among PR-experienced patients who received EBR/GZR + RBV for 16 weeks, an SVR rate of 95% was reported for genotype 1a, while those with a genotype 1b SVR rate of 100% was achieved. Patients with prior treatment experience with DAA who received EBR/GZR + RBV for 12 weeks had a response rate of 96% in patients with genotype 1a and 98% among patients with genotype 1b.

Among treatment-naive patients with genotype 4 who received EBR/GZR for 12 weeks, SVR12 ranged from 90% to 100% (9/10 [90%] in the C-SCAPE trial, 18/18 [100%] in the C-EDGE Treatment-Naive trial, and 27/28 [96.4%] in the C-EDGE Coinfection trial), while in those who were treatment-experienced, the SVR rate was 78% (7/9 [77.8%] in the C-EDGE Treatment-Experienced trial). Treatment-experienced patients who received EBR/GZR + RBV for 16 weeks achieved an SVR rate of 100%. The number of patients with genotype 4 included in the trials was limited; hence, the generalizability of the results is unclear. In addition, the characteristics of the study population were not reported by genotype, and therefore we are not sure if the patient population with genotype 4 is representative of or similar to the population with genotype 4 in Canada.

Only the C-SWIFT trial included patients with genotype 3. Among treatment-naive non-cirrhotic patients, those with genotype 3 who received EBR/GZR + SOF for 12 weeks had a response rate of 100%, while cirrhotic patients had a response rate of 83%, but the number of patients included was limited (14 non-cirrhotic patients and 12 cirrhotic patients), and the generalizability of the results is therefore questionable.

The CDR review protocol also included subgroups by hepatitis B coinfection, and liver transplant; however, such subgroup analyses were not undertaken because patients who would fall into each of these subgroups were excluded from the trial. Hence, the efficacy and safety of EBR/GZR in these subgroups of patients is still unknown.

The included trials reported few cases of relapse. The reported relapses could be associated to the existence of NS5A polymorphisms, where in the C-EDGE Treatment-Naive trial among the 10 genotype 1a–infected patients who experienced virologic failure, nine (90%) had treatment-emergent NS5A RAVs at failure. Seven of the nine patients with treatment-emergent RAVs also had baseline RAVs that cause a greater than five-fold decrease in EBR potency. In the single genotype 1b–infected patient who experienced virologic failure, a treatment-emergent NS5A RAV was detected at failure. Also in the C-EDGE Coinfection trial, the four relapsed patients were assessed for treatment-emergent mutations and it was found that two patients had NS3 and three had NS5A. In addition, the presence of specific NS5A RAVs in genotype 1a patients is associated with a greater than five-fold decrease in EBR in vitro antiviral activity, and may explain the reduced efficacy observed in this subset of patients: 2/9 (22.2%) in the C-EDGE Treatment-Naive trial, 3/4 (75.0%) in the C-EDGE Coinfection trial, and 6/6 (100%) in the C-SURFER trial in treatment-naive patients who received EBR/GZR for 12 weeks, and it was 2/6 (33.3%) in C-EDGE Treatment-Experienced trial in treatment-experienced patients who received EBR/GZR for 12 weeks, and 0/1 (0%) in C-SALVAGE trial in treatment-experienced patients who received EBR/GZR + RBV for 12 weeks; while it was 4/4 (100.0%) in the C-EDGE Treatment-Experienced trial in treatment-experienced patients who received EBR/GZR + RBV for 16 weeks.

Input received from patient groups emphasized the impact that CHC infection has on patients' quality of life. HRQoL was measured using the SF-36, EQ VAS scores, and CLDQ-HCV in the C-EDGE Treatment-Naive, C-EDGE Coinfection, and C-EDGE Treatment-Experienced trials. Other PROs in these trials included the FACIT-F Scale and the WPAI. HRQoL was also measured using the SF-36 and EQ VAS scores in the C-SURFER trial. Across the different PROs, the mean change from baseline in PRO scores during treatment and follow-up did not appreciably differ between EBR/GZR and placebo, whereas in the C-EDGE Treatment-Naive trial, there was no statistically significant difference between EBR/GZR and placebo groups in the vitality, general health, role physical and role emotional domains, and the PCS of the SF-36, EQ-5D VAS scores, Overall CLDQ-HCV, the FACIT-F Scale, and the WPAI. In the C-SURFER trial, the mean changes from baseline in HRQoL scores at treatment week 12 did not differ between the EBR/GZR and placebo groups for vitality, general health, role physical, role emotional, MCS, and PCS of the SF-36. The addition of RBV to EBR/GZR did contribute to a worsening of HRQoL, fatigue levels, and work productivity and activity impairment during treatment. Better HRQoL, less fatigue and less work productivity and activity impairment for EBR/GZR groups were found when compared with the EBR/GZR + RBV groups during the treatment period. At follow-up week 12, HRQoL, fatigue, and work productivity and activity impairment scores were near or better than the baseline scores in patients treated with EBR/GZR plus RBV. It should be noted that most values, particularly those in RBV-free arms, did not deteriorate through treatment, unlike what is typically seen with HRQoL scores from other DAA-based regimens that include PR.[9] Finally, it is worth noting that PROs were exploratory efficacy end points and no formal hypothesis testing was applied; in addition, there were no multiplicity adjustments applied to the PRO variables, and the results of the PRO (CLDQ-HCV, FACIT-F, WPAI, SF-36, and EQ VAS) should therefore be interpreted with caution, where a statistically significant finding for the comparison for these outcomes is more likely subject to inflated type I error rate (alpha). In addition, there was a lack of data imputation for the PROs data when missing. No adjustment for baseline covariates was made in the analysis of differences in mean change from baseline and in the difference between treatment groups. Finally, there is lack of MCIDs specific to CHC, which is a problem for interpretation and lack of validation

in the CHC population for some measures, which could be a potential contributing factor to the inconsistencies in outcomes across the different measures.

Comparative efficacy data are limited due to the lack of an active comparator in the trials and lack of statistical comparisons between treatment arms. The manufacturer did not provide any indirect comparisons in its submission. Despite the evolving standards for conducting a network meta-analysis (NMA) with single-arm data, methodologies for using these data are available, and previous submissions for CHC treatments included indirect comparisons that incorporated single-arm data.[56]

CADTH undertook a therapeutic review that provided estimates of comparative efficacy of different regimens in patients with CHC genotype 1 infection.[57] It was found that in genotype 1 CHC treatment-naive patients, the difference in SVR12 was not statistically significant for EBR/GZR for 12 weeks compared with the following interferon-free regimens: simeprevir plus SOF for 12 weeks, SOF plus RBV for 12 weeks, SOF/ledipasvir for 12 weeks, ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV for 12 weeks, and daclatasvir plus SOF for 12 weeks. Similarly, in genotype 1 CHC treatment-experienced patients, the difference in SVR12 was not statistically significant when EBR/GZR ± RBV for 12 weeks was compared with the following interferon-free regimens: SOF/ledipasvir for 12 weeks, SOF/ledipasvir for 24 weeks, ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV for 12 weeks. Data were limited in the NMA to open-label, uncontrolled (or historically controlled) studies, thus limiting ability to assess comparative efficacy using standard Bayesian indirect comparison methodologies. No individual patient data were available for analyses, so it was not possible to use comparative effectiveness methods, such as propensity scores weighting, for matching studies and identifying a comparator arm or conducting an adjusted analysis. Instead, single-arm studies were incorporated into the NMA by creating a "virtual" study where a comparator arm matched for baseline patient characteristics was identified for the single arm. Additionally, a reference comparison was sometimes not available, or the studies in the NMA were all single arm. A reference treatment was required to statistically connect the treatments for analysis. In these cases, additional studies (meta-analyses [MA], followed by primary observational studies if no MA data available) were identified by clinical experts to be used to provide the required estimates. Because real-world SVR rates for the reference treatments of interest may be lower than those observed in controlled clinical trials, the use of observational study data to bring reference treatments into NMAs may have biased efficacy results in favour of the DAA-containing regimens. The number of trials that contributed to some of the NMAs was limited, which may have reduced the precision of the estimates from these analyses.

### 4.2.2 Harms

Patient group input described adverse events associated with current pegylated interferon–based therapies as severe and debilitating. Hence, it is expected that pegylated interferon–free regimens such as EBR/GZR will be better-tolerated than older regimens containing pegylated interferon. Two included trials, C-EDGE Treatment-Naive and C-SURFER, compared EBR/GZR for 12 weeks with placebo. In C-EDGE Treatment-Naive, EBR/GZR was generally well tolerated, with a similar safety profile in in the active and placebo treatment groups. Serious adverse events were rare, with similar frequencies in the active and placebo groups. Discontinuations for adverse events were likewise uncommon. The most common adverse events were headache, fatigue, and nausea, with similar frequencies in the active and placebo arms. In the C-SURFER trial, in which patients had to have CKD, EBR/GZR was generally well tolerated in the CKD patient population. Overall, the safety profiles of patients who received GZR + EBR in the EBR/GZR and placebo treatment groups were comparable, with similar frequencies of adverse events, serious adverse events, and laboratory abnormalities. Discontinuation of study drug because of adverse events was uncommon in this study population with several comorbidities. There were no adverse

events that led to the discontinuation of the study drug in the EBR/GZR treatment arm; however, five patients in the placebo group (4.4%) had adverse events that led to discontinuation of placebo study drug. Although the overall frequency of adverse events was high, there were no increases in frequency in the EBR/GZR versus placebo treatment group; in addition, as per the clinical expert, these adverse events and serious adverse events are reflective of underlying CKD. The C-EDGE Treatment-Experienced trial included treatment arms with or without RBV, and it was found that the RBV-containing treatment regimens were more poorly tolerated than the non–RBV containing treatment regimens. Fatigue, nausea, vomiting, dyspepsia, rash, and pruritus were observed more frequently in patients treated with RBV. RBV-treated patients were more likely to develop bilirubin elevations and hemoglobin decreases than patients in the RBV-free arms. It is worth noting that serious adverse events were relatively lower than PR-based therapies evaluated in the CADTH therapeutic review of chronic hepatitis C.[9] However, the relative safety of EBR/GZR compared with other available HCV therapies is inconclusive without a direct or indirect comparative evaluation.

## 4.3 Other Considerations

It is worth noting that Health Canada indicated that EBR/GZR may be used as recommended in patients with mild hepatic impairment (Child-Pugh A). EBR/GZR is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B and C) due to the expected significant increase in GZR plasma concentration.[10]

Also, it is worth noting that there is a difference in the duration of treatments between the FDA and Health Canada indications, where the FDA-recommended dosage regimens and durations for EBR/GZR is as follows: a) EBR/GZR for 12 weeks in treatment-naive or PR treatment-experienced patients with genotype 1b infection, in treatment-naive or PR treatment-experienced patients with genotype 1a infection without baseline NS5A polymorphisms, and in genotype 4 treatment-naive patients; b) EBR/GZR + RBV for 12 weeks in PR plus PI treatment-experienced patients with genotype 1a or 1b; and c) EBR/GZR + RBV for 16 weeks genotype 1a treatment-naive or PR-experienced with baseline NS5A polymorphisms, and in genotype 4 PR treatment-experienced patients.[11] In contrast, the Health Canada recommendation was not based on NS5A polymorphisms, but was mainly driven by prior treatment experience. The Health Canada indication was not differentiated between patients who were PR treatment-experienced and patients who were PR plus PI treatment–experienced, unlike the FDA recommendation.[10] On the other hand, the Health Canada reviewer report indicated that in patients with genotype 1, baseline NS3 RAVs were not associated with SVR12 but greater than five-fold NS5A RAVs to EBR obviously impacted the SVR12 and the trend was more likely with high viral load of the virus combined.[12] Baseline resistance testing is not currently routinely done in Canada.

## 4.4 Potential Place in Therapy[1]

The last one and a half years have marked an exciting new era for patients with HCV with the introduction of all oral DAAs in Canada. In the majority of patients, this has provided cure rates in the range of 90% to 98%. However, for some genotypes (2 and 3), reimbursement is a challenge, and for genotype 4 to 6, DAAs are not approved for all patient types.

For EBR/GZR, in genotype 1 treatment-naive patients and relapsers, a 12-week regimen is indicated. In genotypes 1 and 4 in PR or PR+PI on-treatment virologic failures, 16 weeks with RBV is required. In genotype 1b treatment-naive patients METAVIR stage F0-F2 fibrosis, a shortened eight-week regimen

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

may be utilized. In genotype 3, only treatment-naive patients can be treated with the addition of SOF. There is a limited study population (26 persons) for persons with genotype 3. Although it is likely that this regimen will be very effective in genotype 3 patients, further data on this combination would be beneficial. EBR/GZR is contraindicated in persons with moderate or severe liver dysfunction (Child-Pugh B and C patients).

EBR/GZR is highly effective for persons with genotype 1a, although it appears that those with certain baseline NS5A RAVs to EBR at potency > 5 limits the effectiveness when this regimen is used for 12 weeks. In the FDA label,[11] if these RAVs are present, therapy should be extended to 16 weeks with RBV to provide optimal SVRs. In circumstances where baseline RAV testing is easily available, this regimen can be used with even greater certainty of a high SVR (> 98%). Other regimens utilizing a NS5A DAA also have an effect of baseline NS5A RAVs lowering their SVR.

While the efficacy and tolerability of this regimen is similar to others available,[8,27-29,31,32] there are certain patient populations in which it addresses an unmet medical need. Specifically, in genotype 1 persons with severe renal impairment (GFR </= 30 mL/min.) and/or on hemodialysis, GZR and EBR can be utilized without dose adjustment. If utilized for genotype 3 patients, it should be combined with SOF, for which renal dosing adjustment is not well established.

For persons with genotype 4, this is the first RBV-free DAA-approved regimen for both cirrhotic and non-cirrhotic patients. Paritaprevir/ritonavir/ombitasvir with ribavirin has recently been approved by Health Canada for genotype 4 non-cirrhotic patients.[32]

Drug–drug interactions are frequent with the available HCV regimens. While EBR/GZR continues to have some drug–drug interactions, they are fewer overall and to some degree have different drug–drug interactions compared with present regimens. This provides more options in treating persons with comorbidities.

# 5. CONCLUSIONS

Based on data from eight trials (two randomized, double-blind, placebo-controlled trials that also compared EBR/GZR versus a historical control; two trials that compared EBR/GZR versus a historical control; and four uncontrolled, open-label trials), EBR/GZR was associated with high rates of SVR12 in patients with genotype 1 or 4 CHC infection, in both treatment-naive and treatment-experienced patients; in addition, a high SVR12 rate was reported in treatment-naive patients with genotype 1 or 4 CHC infection who were coinfected with HIV. In addition, EBR/GZR was associated with high rates of SVR12 in treatment-naive and treatment-experienced patients with genotype 1 CHC infection who have CKD. These SVR12 rates were higher than SVR12 rates reported for the historical comparator simeprevir plus PR, sofosbuvir plus RBV, and PR. In addition, when combined with sofosbuvir, EBR/GZR was associated with high rates of SVR12 in treatment-naive patients with genotype 3. The data were limited for some populations, specifically patients with genotype 3 or 4 CHC. HRQoL measures showed clinically insignificant changes from baseline, and differences between treatment groups and with treatment groups in each trial were inconsistent between the different HRQoL measures. Serious AEs and withdrawals due to AEs were very limited, indicating good tolerability of the evaluated medication. Characteristic AEs associated with pegylated interferon appeared to occur less frequently among patients treated with EBR/GZR. However, the relative efficacy and safety of EBR/GZR compared with more recent interferon-free HCV therapies is uncertain because of the absence of direct or indirect comparative evaluations.

# APPENDIX 1: PATIENT INPUT SUMMARY

*This section was prepared by CADTH staff based on the input provided by patient groups.*

### 1. Brief Description of Patient Group(s) Supplying Input

A total of five groups submitted patient input.

The Canadian Liver Foundation (CLF) is a national organization committed to reducing the incidence and impact of liver disease for Canadians living with or at risk of liver disease, through research, public and professional education programs, patient support programs, and other fundraising and outreach efforts. The CLF has received unrestricted educational grants and/or has worked on joint initiatives with AbbVie Corporation, Astellas Pharma Canada Inc., Boehringer Ingelheim (Canada) Inc., Gilead Sciences Canada Inc., Janssen Inc., Merck Canada Inc., Novartis Pharmaceuticals Canada Inc., and Hoffmann-La Roche Limited. In addition, Dr. Sherman, Chairperson of the CLF, has received honorariums from AbbVie Corporation, Boehringer Ingelheim (Canada) Inc., Merck Canada Inc., Janssen Inc., Hoffmann-La Roche Limited, Gilead Sciences Canada Inc., Vertex, and Bristol-Myers Squibb.

The Gastrointestinal (GI) Society is a Canadian leader in providing trusted, evidence-based information on all areas of the gastrointestinal tract, and is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to health care, and promoting gastrointestinal and liver health. The GI Society receives financial contributions from pharmaceutical companies in support of its independent charitable work for Canadians affected by gastrointestinal and/or liver conditions. Supporters have no input into the editorial content of its resource material. The GI Society receives funding from Merck, but did not for the completion of this document, or any related issue. It declared no conflicts of interest in the preparation of this submission.

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization whose mandate is to address access to treatment, care, and support for people living with HIV or hepatitis C virus (HCV). Full membership is limited to persons living with HIV/AIDS or organizations with a substantial HIV/AIDS mandate. CTAC received unrestricted organizational and/or educational grants from the following organizations in the 2014-2015 fiscal year: Abbott/AbbVie, Gilead Sciences, Janssen, and ViiV Healthcare.

The Pacific Hepatitis C Network's mission is to strengthen the capacity of individuals and organizations throughout British Columbia to prevent new HCV infections and to improve the health and treatment outcomes of people already living with HCV. Its members include individuals at risk, exposed to, or concerned about HCV. The Pacific Hepatitis C Network has received one-time project grants from AbbVie Corporation, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, and Merck Canada for the "Hepatitis C Treatment Information Project," an online HCV treatment information resource. It declared no conflicts of interest in the preparation of this submission.

Hepatitis C Education and Prevention Society (HepCBC) is a non-profit organization run by and for people affected by HCV in British Columbia. It focuses on providing peer support groups, anti-stigma activities, prevention education, general hepatitis information, and encouraging testing among at-risk groups among other activities. HepCBC has received funding for hepatitis C–oriented projects such as publishing educational materials, organizing educational forums, attending and presenting at educational conferences, advertising in newspapers and on buses (events and hepatitis C patient

awareness), and holding awareness activities from the following pharmaceutical companies over the last four years: Merck Pharmaceuticals, Hoffman-La Roche, Vertex Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, and AbbVie, plus support from Rx&D, the pharmaceutical umbrella organization.

## 2. Condition-Related Information

The information was gathered through interviews with patients and caregivers affected by hepatitis C, nurse specialists, gastroenterologists, hepatologists, and pharmacists, through surveys and meetings with support groups and via a webinar that included patients diagnosed with hepatitis C.

HCV is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, cancer, liver failure and even death. For those coinfected with HIV, liver disease progression may be exacerbated. Furthermore, coinfected patients express additional psychological emotional and physical distress, as many of their respective medications impact one another. Some patients have few or no symptoms, but others experience fatigue; general weakness; abdominal, muscle, or joint pain; itchiness; poor circulation; constipation; diarrhea; nausea; headaches; loss of appetite; sensitivity to light or food; portal hypertension; reflex impairment; psoriasis; peripheral neuropathy; osteopenia; disrupted sleep; and jaundice. In some patients, the disease affects their cognitive functions and they find it difficult to function when their thinking, understanding, memory, or focus is impeded. The fatigue and other symptoms may be severe and can limit patients' ability to work, manage their home, care for family members, and maintain friendships. According to patient groups, it was described as "a disease that affects all aspects of life before it takes it."

Patients must cope with the stigma associated with HCV and are often reluctant to disclose their HCV status for fear of rejection, discrimination, or ostracism. The social stigma, fear of spreading the infection, and the uncertainty regarding their future health exact a high emotional toll on patients that may lead to anger, depression, anxiety, loss of hope, and social isolation. Often marriages and other personal relationships cannot survive the strain. To patients, a cure means freedom from debilitating fatigue and stigma-centred fear, and optimism about their health.

Spouses and loved ones who care for patients with HCV are faced with a substantial burden, as the symptoms of HCV can leave the patient completely dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, the relationship, or the care of children. Caregivers must endure their loved one's mood swings, dietary problems, and lack of energy and concentration while shouldering the responsibility for managing doctor's appointments, drug regimens, and household responsibilities. As the patient's symptoms and behaviour become more difficult to manage, families and marriages can break apart due to stress, financial difficulties, and social isolation.

### 3. Current Therapy-Related Information

Current therapy can be long and gruelling and usually involves weekly injections of pegylated interferon accompanied by ribavirin (PR; six to eight pills per day) for up to 48 weeks. This treatment may include boceprevir or telaprevir, which increases pill burden and side effects. The adverse events caused by the current standard therapies can be severe and debilitating, such as extreme fatigue, anemia, depression, anxiety, mood swings, rashes, insomnia, cognitive impairment, irritability, memory loss, headaches, hearing loss, chills, nausea, weight loss, suppressed appetite, hair loss, and joint pain. In addition, some therapy regimens require patients to take up to 20 pills throughout the day, with specific food requirements, and have adverse drug interactions with antiretroviral therapies (i.e., patients coinfected with HIV). The adverse events of treatment may affect patients' ability to continue working and to

manage their household, childcare and relationships. In addition to the plethora of side effects with current standard therapy, patients have no way of knowing if the treatments will be successful and if their efforts to complete therapy will be worth it. Patients have also reported that the injections associated with interferon can be a triggering factor and a source of anxiety for those with a history of injection drug use. According to patient groups, the debilitation due to the adverse events, regimen burden, tolerance, and success rate of the current standard therapy causes HCV patients to delay treatment until necessary or causes withdrawal from current treatment.

The side effects of current standard therapy for hepatitis C can leave patients completely dependent and unable to contribute financially, physically, or emotionally, and therefore the burden falls on the caregiver (often family) to compensate. Patient groups suggest that the burden extends beyond the direct caregiver and includes everyone in the HCV patient's social circle (family, friends, and coworkers) to help support them during treatment. For caregivers, the challenges associated with caring and achieving a cure for hepatitis C patients are significant. They have described caring for an HCV patient undergoing treatment as a relentless and ongoing task. Patient groups identify the following roles and responsibilities for those giving care to HCV patients: education and counsel about currently available treatment options, and the management of medical appointments and drug regimens. Caregivers also expressed some of the consequences associated with the debilitation of patients caused by HCV treatments, such as depression, increased family obligations, financial worries, social isolation, lack of social support, absenteeism from work, increased household responsibilities, stress, tiredness, resentment, and guilt. In addition, patient groups have also expressed the concerns of caregivers with respect to the possibility of HCV infection. Caregivers continuously emphasize their helplessness with respect to the health and future of HCV patients, as well as the need for new treatment options to reduce the hardships of treatment failure or ineligibility.

Many patients have contraindications or cannot tolerate interferon and thus are ineligible for interferon-based regimens. Those who have failed interferon-based treatments have few treatment options. Patient groups mention optimism and excitement for novel interferon-free direct-acting antiviral agents (DAAs) for HCV treatment, especially for those that are hard to treat, such as patients who have failed standard therapy, those who have contraindications or cannot tolerate interferon, those coinfected with HIV, those with kidney impairment, those with compensated cirrhosis, and those infected with rare and/or multiple HCV genotypes.

### 4. Expectations About the Drug Being Reviewed

According to patient groups, the general expectations of novel HCV treatments are reduced suffering (adverse events and regimen burden), interferon-free oral DAA regimens, greater treatment success rates (i.e., sustained virologic response [SVR]) and shorter treatment regimens. Patients suggest that if these expectations are met, it would translate to fewer hardships (require less mental and physical support) and would result in improved treatment adherence. Elbasvir/grazoprevir (EBR/GZR) is an interferon-free DAA anticipated to receive a Health Canada indication for the treatment of adults infected with CHC genotypes 1, 3, 4, or 6. The regimen requires one pill a day for as few as 12 weeks and has no stringent food requirements.

The expectations for EBR/GZR are that it will address the gap in treatment and unmet needs of HCV patients, such as null response or relapse patients, those who have contraindications or cannot tolerate interferon, those coinfected with HIV, those with kidney impairment, those with compensated cirrhosis, and those infected with rare and/or multiple HCV genotypes. Patients also have high expectations of a cure with EBR/GZR. Once cured, they expect that their fibrosis or cirrhosis will reverse, and their risk of

end-stage liver disease will be reduced. Patients state that they are looking to receive treatment as early as possible, regardless of their disease status. The accessibility and affordability of EBR/GZR is of great concern to HCV patients.

Respondents were encouraged about the availability of this drug for the following reasons: frequency of SVR of 95% or greater, the limited treatment options currently available, reduced adverse events, reduced regimen burden, and the fact that the treatment is interferon-free. Additionally, patients are pleased with the short treatment timeframe, further minimizing potential side effects and the chances for inadvertently spreading the disease. Decreasing treatment time is a priority for patients and health care providers due to its impact on treatment adherence and side effects, and on expediting patients' return to their normal lives. Patient groups report that personal and professional relationships will improve and the stigma of the disease will decrease if EBR/GZR is accessible and affordable. Based on feedback from treatment-experienced individuals, EBR/GZR was easy to administer and tolerate. Two patients report that their viral count was 0 at or before the end of treatment. They also reported that side effects were minimal (abdominal pain, anemia, fatigue, and rash) and were more manageable than expected or compared with previous treatments. Some express that they may be able to think clearly, return to work, and have intimate contact with others, and that the overall quality of life of everyone will improve. Patients groups suggest that its low toxicity and lack of drug interactions cause fewer side effects than previous interferon-containing treatments, and therefore treatment with EBR/GZR will likely require far less clinical management, fewer hospital visits, and less time off work, reducing the impact on quality of life.

## 5. Additional Information

Patients are concerned that the prices of EBR/GZR will be high like other drugs in its class and that it will not get approved, or that the coverage criteria will require patients to undergo and fail very challenging standard treatments (with both interferon and ribavirin) before treatment access to EBR/GZR is granted. Delaying treatment until liver disease is more advanced impacts patients' physical and mental well-being. Patients find it frustrating, especially those who are experiencing multiple barriers, to be told that they are not sick enough to qualify for treatment. Patients worry about the liver damage that may be caused by delaying treatment. The sooner a person is effectively treated (i.e., cured), the less chance they have of inadvertently infecting someone else. Patients note that all those infected with HCV are not homogenous and cannot be treated as such. Customized treatments are necessary to achieve the best possible outcomes based on patient needs, and would require more treatment options to be accessible. Improved treatments for HCV have the potential to reduce social system and health care costs for patients with severe liver disease. Patients also have concerns that this treatment will not be accessible because it is either not covered by public drug plans or the criteria for coverage will limit access. As a result, patients would prefer that this treatment is offered to all people with HCV, regardless of the patients' severity of liver damage.

# APPENDIX 2: LITERATURE SEARCH STRATEGY

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | Embase 1974 to present<br>MEDLINE Daily and MEDLINE 1946 to present<br>MEDLINE In-Process & Other Non-Indexed Citations<br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | November 26, 2015 |
| Alerts: | Monthly search updates until April 20, 2016 |
| Study Types: | No search filters were applied |
| Limits: | No date or language limits were used<br>Conference abstracts were excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| .ti | Title |
| .ab | Abstract |
| .ot | Original title |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .kw | Author keyword (Embase) |
| .pt | Publication type |
| .rn | CAS registry number |
| .nm | Name of substance word |
| pmez | Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present |
| oemezd | Ovid database code; Embase 1974 to present, updated daily |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **#** | **Searches** |
| 1 | (1350462-55-3 or 1350514-68-9 or 1206524-75-5 or 1356446-42-8).rn,nm. or (grazoprevir* or 4O2AB118LA or 8YE81R1X1J or MK 5172 or MK5172).ti,ab,ot,kw,hw,rn,nm. |
| 2 | (1370468-36-2 or 1444832-51-2).rn,nm. or (elbasvir* or 632L571YDK or MK 8742 or MK8742).ti,ab,ot,kw,hw,rn,nm. |
| 3 | 1 and 2 |
| 4 | 3 use pmez |
| 5 | *grazoprevir/ or (grazoprevir* or 4O2AB118LA or 8YE81R1X1J or MK 5172 or MK5172).ti,ab. |
| 6 | *elbasvir/ or (elbasvir* or 632L571YDK or MK 8742 or MK8742).ti,ab. |
| 7 | 5 and 6 |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **#** | **Searches** |
| 8 | 7 use oemezd |
| 9 | ("GZR/EBR" or (GZR adj EBR) or (GZR and EBR)).ti,ab. |
| 10 | 4 or 8 or 9 |
| 11 | 10 not conference abstract.pt. |
| 12 | remove duplicates from 11 |

| OTHER DATABASES | |
|---|---|
| PubMed | A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. |
| Trial registries (Clinicaltrials.gov and others) | Same keywords, limits used as per MEDLINE search. |

**Grey Literature**

| | |
|---|---|
| Dates for Search: | November 2015 |
| Keywords: | grazoprevir, elbasvir, Hepatitis C |
| Limits: | No date or language limits used |

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: A practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

# APPENDIX 3: EXCLUDED STUDIES

| Reference | Reason for Exclusion |
|---|---|
| Lagging et al., 2016[58] | Inappropriate regimen |
| Corrections to C-EDGE Coinfection[59] | Corrections, erratum |
| Roth et al., 2015[60] | Corrections, erratum |
| Corrections C-EDGE Coinfection[61] | Corrections, erratum |

# APPENDIX 4: DETAILED OUTCOME DATA

**TABLE 14: SUMMARY OF SUSTAINED VIROLOGIC RESPONSE**

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11) | EBR/GZR for 12 Weeks (n = 111) | PBO 12 Weeks (n = 113) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12) |
| **SVR12 (full analysis set)** | | | | | | | | | | |
| N (%)<br>[95% CI] | 299 (94.6)<br>[91.5 to 96.8] | NR | 207 (95.0)<br>[91.2 to 97.5][a] | 115/122 (94.3)<br>[88.5 to 97.7] | | NR | 97 (92.4)<br>[85.5 to 96.7] | 103 (97.2)<br>[92.0 to 99.4] | 14 (100.0)<br>[76.8 to 100] | 10 (83.3)<br>[51.6 to 97.9] |
| Difference (95% CI) | NR | | | NR | | | NR | | NA | NA |
| Superiority achieved[b] | Yes | NA | Yes | Yes | | NA | Yes | Yes | NA | NA |
| **SVR12 (PP population)** | | | | | | | | | | |
| n/N (%)<br>[95% CI] | 299/313 (95.5)<br>[92.6 to 97.5] | NR | 207/214 (96.7)<br>[93.4 to 98.7] | 114/115 (99.1)<br>[95.3 to 100] | | NR | 97/102 (95.1)<br>[88.9 to 98.4] | 101/101 (100)<br>[96.4 to 100.0] | 14(100.0)<br>[76.8 to 100] | 10/11 (90.9)<br>[58.7 to 99.8] |
| Difference (95% CI) | NR | | NA | NR | | | NR | | NA | NA |
| Superiority achieved | Yes | NA | Yes | Yes | | NA | Yes | Yes | NA | NA |
| **SVR12 (modified full analysis set)[c]** | | | | | | | | | | |
| N (%)<br>[95% CI] | NR | NR | NR | 115/116 (99.1)<br>[95.3 to 100.0] | | NR | NR | NR | NR | NR |
| Difference (95% CI) | NR | NR | NR | NR | | | NR | NR | NR | NR |
| Superiority achieved | NR | NR | NR | Yes | | NA | NR | NR | NR | NR |
| **SVR12 by genotype (full analysis set)[d]** | | | | | | | | | | |
| GT 1a, n/N (%) | 144/157 (91.7) | NR | 136/144 (94.4)[a] | 61/61 (100)[c] | | NR | 55/61 (90.2) | 55/58 (94.8) | NA | NA |
| GT 1b, n/N (%) | 129/131 (98.5) | | 42/44 (95.5) | 54/55 (98.2)[c] | | | 34/34 (100) | 36/36 (100) | NA | NA |
| GT 1 other | NA | | 1/1 (100) | NR | | | 1/1 (100) | 2/2 (100) | NA | NA |
| GT 3, n/N (%) | NA | | NA | NA | | NA | NA | NA | 14/14 (100) | 10/12 (83.3) |
| GT 4, n/N (%) | 18/18 (100) | | 27/28 (96.4) | NA | NA | NA | 7/9 (77.8) | 8/8 (100) | NA | NA |
| **SVR12 by fibrosis stage (full analysis set)** | | | | | | | | | | |
| Non-cirrhotic, n/N (%) | 231/246 (93.9) | NR | 172/183 (94.0) | 109/110 (99.1)[c] | | NR | 64/68 (94.1) | 66/69 (95.7) | 14/14 (100) | 0 |
| Cirrhotic, n/N (%) | 68/70 (97.1) | | 35/35 (100) | 6/6 (100)[c] | | | 33/37 (89.2) | 37/37 (100) | 0 | 10/12 (83.3) |
| GT 1a Non-cirrhotic, n/N (%) | 112/123 (91.1) | | NR | NR | | | NR | NR | NR | NR |

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11) | EBR/GZR for 12 Weeks (n = 111) | PBO 12 Weeks (n = 113) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12) |
| GT 1a Cirrhotic, n/N (%) | 32/34/(94.1) | | | | | | NR | NR | NR | NR |
| GT 1b Non-cirrhotic, n/N (%) | 95/97 (97.9) | | | | | | NR | NR | NR | NR |
| GT 1b Cirrhotic, n/N (%) | 34/34 (100) | | | | | | NR | NR | NR | NR |
| GT 4 Non-cirrhotic, n/N (%) | 16/16 (100) | | | NA | | NA | NR | NR | NR | NR |
| GT 4 Cirrhotic, n/N (%) | 2/2 (100) | | | | | | NR | NR | NR | NR |
| **SVR12 by Interferon treatment eligibility status (full analysis set)** | | | | | | | | | | |
| Eligible | 293/310 (94.5) | NR | 183/194 (94.3) | NR | NR | NR | NR | NR | NR | NR |
| Ineligible | 6/6 (100) | | 11/11 (100) | NR | NR | NR | NR | NR | NR | NR |
| Naive — interferon unwilling | NR | | 13/13 (100) | NR | NR | NR | NR | NR | NR | NR |
| **SVR12 by Baseline HCV RNA (full analysis set)** | | | | | | | | | | |
| ≤ 800,000 IU/mL) | 94/94 (100) | NR | 88/91 (96.7) | 50/50 (100)[c] | | NR | 23/24 (95.8) | 28/28 (100) | 8/8 (100) | 4/4 (100) |
| > 800,000 IU/mL) | 205/222 (92.3) | | 119/127 (93.7) | 65/66 (98.5)[c] | | | 74/81 (91.4) | 75/78 (96.2) | 6/6 (100) | 6/8 (75.0) |
| **SVR12 by Prior HCV treatment status (full analysis set)** | | | | | | | | | | |
| Naive | 299 (94.6) | NR | 207 (95.0) | 96/96 (100)[c] | | NR | NA | NA | 14/14 (100) | 10/12 (83.3) |
| Treatment-experienced | NA | NA | NA | 19/20 (95.0)[c] | | | 97/105 (92.4) | 103/106 (97.2) | NA | NA |
| **SVR12 by Prior treatment response** | | | | | | | | | | |
| Null responder | NA | NA | NA | NR | | NR | 45/49 (91.8) | 41/43 (95.3) | NA | NA |
| Partial responder | NA | NA | NA | NR | | NR | 17/21 (81.0) | 22/23 (95.7) | NA | NA |
| Relapser | NA | NA | NA | NR | | NR | 35/35 (100) | 40/40 (100) | NA | NA |
| **SVR12 by Coinfected with HIV (full analysis set)** | | | | | | | | | | |
| GT 1a | NA | NA | 136/144 (94.4) | NA | NA | NA | NR | NR | NA | NA |
| GT 1b | NA | NA | 42/44 (95.5) | NA | NA | NA | NR | NR | NA | NA |
| GT 4 | NA | NA | 27/28 (96.4) | NA | NA | NA | NR | NR | NA | NA |
| All HIV-coinfected patients | NA | NA | 207/218 (95.0) | NA | NA | NA | 6/6 (100) | 4/4 (100) | NA | NA |
| **SVR12 by ARV therapy with NRTI backbone (full analysis set)** | | | | | | | | | | |
| Abacavir-containing regimen | NA | NA | 43/47 (91.5) | NA | NA | NA | NR | NR | NA | NA |
| Tenofovir-containing regimen | NA | NA | 158/164 (96.3) | NA | NA | NA | NR | NR | NA | NA |

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11) | EBR/GZR for 12 Weeks (n = 111) | PBO 12 Weeks (n = 113) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12) |
| **SVR12 by ARV therapy with 3rd agent in ARV regimen (full analysis set)** | | | | | | | | | | |
| Raltegravir | NA | NA | 107/113 (94.7) | NA | NA | NA | NR | NR | NA | NA |
| Dolutegravir | NA | NA | 58/59 (98.3) | NA | NA | NA | NR | NR | NA | NA |
| Rilpivirine | NA | NA | 36/38 (94.7) | NA | NA | NA | NR | NR | NA | NA |
| **SVR12 by Dialysis status at baseline** | | | | | | | | | | |
| On dialysis | NR | NR | NR | 86/87 (98.9)[c] | | NR | NR | NR | NR | NR |
| Not on dialysis | NR | NR | NR | 29/29 (100)[c] | | | NR | NR | NR | NR |
| **SVR12 by CKD stage at baseline** | | | | | | | | | | |
| Stage 4 | NA | NA | NA | 22/22 (100)[c] | | NR | NR | NR | NR | NR |
| Stage 5 | NA | NA | NA | 93/94 (98.9)[c] | | | NR | NR | NR | NR |
| **SVR12 by Signature NS5A RAVs at baseline, n/N (%)** | | | | | | | | | | |
| **Genotype 1a** | | | | | | | | | | |
| None detected by population sequencing | 133/135 (98.5) | NR | 127/130 (97.7) | 54/54 (100)[c] | | NR | 49/50 (98.0) | 49/49 (100.0) | NR | NR |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | 9/10 (90.0) | | 5/6 (83.3) | 1/1 (100)[c] | | | 4/4 (100.0) | 2/2 (100.0) | NR | NR |
| NS5A RAVs with > 5x elevation in EBR $EC_{50}$ | 2/9 (22.2) | | 3/4 (75.0) | 6/6 (100)[c] | | | 2/6 (33.3) | 4/4 (100.0) | NR | NR |
| **Genotype 1b** | | | | | | | | | | |
| None detected by population sequencing | 112/112 (100) | | 37/38 (97.4) | 44/44 (100)[c] | | | 32/32 (100.0) | 33/33 (100.0) | NR | NR |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | 1/1 (100) | | 0/0 (NA) | 0/0 (NA) | | | 0/0 (NA) | 0/0 (NA) | NR | NR |
| NS5A RAVs with > 5x elevation in EBR $EC_{50}$ | 16/17 (94.1) | | 5/5 (100) | 9/10 (90)[c] | | | 2/2 (100.0) | 3/3 (100.0) | NR | NR |
| **Genotype 4** | | | | | | | | | | |
| None detected by population sequencing | 9/9 (100) | | 16/17 (94.1) | NA | | | 6/7 (85.7) | 4/4 (100) | NR | NR |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | 9/9 (100) | | 11/11 (100) | NA | | | 1/1 (100) | 4/4 (100) | NR | NR |
| NS5A RAVs with > 5x elevation in EBR $EC_{50}$ | | | | NA | | | | | NR | NR |

| | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) (n = 11) | EBR/GZR for 12 Weeks (n = 111) | PBO 12 Weeks (n = 113) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) (n = 14) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) (n = 12) |
| **Virologic breakthrough (full analysis set)** | | | | | | | | | | |
| GT 1a | 1/157 (0.6) | NR | 0 | 0 | | NR | 0 | 0 | NA | NA |
| GT 1b | 0 | | 0 | 0 | | | 0 | 0 | NA | NA |
| GT 4 | 0 | | 0 | NA | NA | NA | 0 | 0 | NA | NA |
| **Relapse (full analysis set)** | | | | | | | | | | |
| GT 1a | 9/157 (5.7) | NR | 5/144 (3.5) | 0 | | NR | 5 (8.2) | 0 | NA | NA |
| GT 1b | 1/131 (0.8) | NR | 1/44 (2.3) | 1/55 (1.8)[c] | | | 0 | 0 | NA | NA |
| GT 3 | NA | NA | NA | NA | | NA | NA | NA | 0 | 1 (8.3) |
| GT 4 | 0 | NR | 1/28 (3.6) | NA | NA | NA | 1 (11.1) | 0 | NA | NA |

ARV = antiretroviral; CI = confidence interval; CKD = chronic kidney disease; EC50 = effective concentration necessary to inhibit a replicon; EBR = elbasvir; GT = genotype; GZR = grazoprevir; HCV = hepatitis C virus; ITT = intention-to-treat; NA = not applicable; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitor; NS5A = nonstructural protein 5A; OL = open-label; PBO = placebo; PK = pharmacokinetic; PP = per-protocol; RAV = resistance-associated variant; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; Sup = superiority; SVR = sustained virologic response.

[a] In the article by Rockstroh et al.,[34] it was reported that 210 (96.3%) of the 218 patients achieved SVR12, with a 95% CI of (92.9%, 98.4%), while the number of patients with genotype 1a who achieved SVR12 was 139 (96.5%) out of 144.

[b] Superiority was determined by the lower bound of the 95% CI surpassing the reported historical control rate.

[c] The modified full analysis set population is a subset of the FAS population with patients excluded for the following reasons: failure to receive at least one dose of active study treatment, missing data due to death with reasons unrelated to study drug or reasons other than liver disease, and missing data due to study discontinuation with reasons unrelated to progression of liver disease, study drug and their responses to the HCV treatment.

[d] GT 6 results are not reported because this regimen is not currently indicated for this population.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SWIFT;[14] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 14: SUMMARY OF SUSTAINED VIROLOGIC RESPONSE, CONTINUED**

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT 1b: EBR/GZR for 12 Weeks (n = 13)** | **TN NC GT 1a: EBR/GZR for 12 Weeks (n = 31)** | **TN NC GT 1b: EBR/GZR for 8 Weeks (n = 31)** | **TN HIV NC GT 1: EBR/GZR for 12 Weeks (n = 30)** | **TN C GT 1: EBR/GZR for 12 Weeks (n = 29)** | **Null responder GT 1: EBR/GZR for 12 Weeks (n = 33)** | **EBR/GZR + RBV for 12 Weeks (n = 79)** | **EBR/GZR for 12 Weeks (n = 19)** |
| **SVR12 (full analysis set)** | | | | | | | | |
| N (%)<br>[95% CI] | 13 (100.0)<br>[75.3 to 100.0] | 30 (96.8)<br>[83.3 to 99.9] | 29 (93.5)<br>[78.6 to 99.2] | 26 (86.7)<br>[69.3 to 96.2] | 28 (96.6)<br>[82.2 to 99.9] | 30 (90.9)<br>[75.7 to 98.1] | 76 (96.2)<br>[89.3 to 99.2] | 9/10 (90.0)<br>[55.5 to 99.7][a] |
| **SVR12 (PP population)** | | | | | | | | |
| n/N (%)<br>[95% CI] | 12/12 (100.0)<br>[73.5 to 100.0] | 30/31 (96.8)<br>[83.3 to 99.9] | 29/31 (93.5)<br>[78.6 to 99.2] | 26/28 (92.9)<br>[76.5 to 99.1] | 28/29 (96.6)<br>[82.2 to 99.9] | 30/33 (90.9)<br>[75.7 to 98.1] | 68/70 (97.1)<br>[90.1 to 99.7] | 7/7 (100.0)<br>[59.0 to 100.0][a] |
| **SVR24 (full analysis set)** | | | | | | | | |
| N (%)<br>[95% CI] | 13 (100.0)<br>(75.3 to 100.0) | 30 (96.8)<br>(83.3 to 99.9) | 29 (93.5)<br>(78.6 to 99.2) | 24 (80.0)<br>(61.4 to 92.3) | 28 (96.6)<br>(82.2 to 99.9) | 30 (90.9)<br>(75.7 to 98.1) | 76 (96.2)<br>[89.3 to 99.2] | NR |
| **SVR12 by genotype (full analysis set)** | | | | | | | | |
| GT 1a, n/N (%) | NA | 29/30 (96.7) | NA | 19/22 (86.4) | 19/20 (95.0) | 20/22 (90.9) | 28/30 (93.3) | NA |
| GT 1b, n/N (%) | 13/13 (100.0) | 1/1 (100.0) | 29/31 (93.5) | 7/8 (87.5) | 7/7 (100) | 10/11 (90.9) | 48/49 (98.0) | NA |
| GT 1 other | NA | NA | NA | NA | 2/2 (100) | NA | NA | NA |
| GT 4, n/N (%) | NA | NA | NA | NA | NA | NA | NA | 9/10 (90.0) |
| **SVR12 by fibrosis stage (full analysis set)** | | | | | | | | |
| NC, n/N (%) | 13/13 (100.0) | 30/31 (96.8) | 29/31 (93.5) | 26/30 (86.7) | NA | NR | 44/45 (97.8) | NA |
| C, n/N (%) | NA | NA | NA | NA | 28/29 (96.6) | NR | 32/34 (94.1) | NA |
| GT 4 NC, n/N (%) | NA | NA | NA | NA | NA | NA | NA | 9/10 (90.0) |
| **SVR12 by METAVIR score** | | | | | | | | |
| F0 to F2, n/N (%) | 13/13 (100) | 25/26 (96.2) | 28/29 (96.6) | 23/27 (85.2) | 0 | 14/16 (87.5) | NR | NR |
| F3, n/N (%) | 0 | 5/5 (100) | 1/2 (50.0) | 3/3 (100) | 0 | 3/3 (100) | NR | NR |
| F4, n/N (%) | 0 | 0 | 0 | 0 | 28/29 (96.6) | 13/14 (92.9) | NR | NR |
| **SVR12 by Baseline HCV RNA (full analysis set)** | | | | | | | | |
| ≤ 800,000 IU/mL), n/N (%) | 6/6 (100) | 5/5 (100) | 4/4 (100) | 5/5 (100) | 4/4 (100) | 1/1 (100) | 27/29 (93.1) | NR |
| > 800,000 IU/mL), n/N (%) | 7/7 (100) | 25/26 (96.2) | 25/27 (92.6) | 21/25 (84.0) | 24/25 (96.0) | 29/32 (90.6) | 49/50 (98.0) | NR |

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT 1b: EBR/GZR for 12 Weeks (n = 13)** | **TN NC GT 1a: EBR/GZR for 12 Weeks (n = 31)** | **TN NC GT 1b: EBR/GZR for 8 Weeks (n = 31)** | **TN HIV NC GT 1: EBR/GZR for 12 Weeks (n = 30)** | **TN C GT 1: EBR/GZR for 12 Weeks (n = 29)** | **Null responder GT 1: EBR/GZR for 12 Weeks (n = 33)** | **EBR/GZR + RBV for 12 Weeks (n = 79)** | **EBR/GZR for 12 Weeks (n = 19)** |
| **SVR12 by Prior HCV treatment status (full analysis set)** | | | | | | | | |
| Naive | 13 (100.0) | 30 (96.8) | 29 (93.5) | 26 (86.7) | 28 (96.6) | NA | NA | 9/10 (90.0) |
| Treatment-experienced | NA | NA | NA | NA | NA | 30 (90.9) | 76 (96.2) | NA |
| Prior treatment response | | | | | | | | |
| Null responder | NA | NA | NA | NA | NA | 30 (90.9) | 16/16 (100) | NA |
| Partial responder | NA | NA | NA | NA | NA | NA | | NA |
| Relapser | NA | NA | NA | NA | NA | NA | 25/26 (96.2) | NA |
| PR + DAA breakthrough | NA | NA | NA | NA | NA | NA | 8/8 (100) | NA |
| PR TAIL breakthrough | NA | NA | NA | NA | NA | NR | 14/16 (87.5) | NA |
| Other[b] | NA | NA | NA | NA | NA | NR | 13/13 (100) | NA |
| **SVR12 by Prior DAA** | | | | | | | | |
| Boceprevir | NA | NA | NA | NA | NA | NA | 27/28 (96.4) | NA |
| Telaprevir | NA | NA | NA | NA | NA | NA | 41/43 (95.3) | NA |
| Simeprevir | NA | NA | NA | NA | NA | NA | 8/8 (100) | NA |
| **SVR12 by Coinfected with HIV (full analysis set)** | | | | | | | | |
| GT 1a | NA | NA | NA | 19/22 (86.4) | NA | NA | NA | NA |
| GT 1b | NA | NA | NA | 7/8 (87.5) | NA | NA | NA | NA |
| **SVR12 by Signature NS5A RAVs at baseline** | | | | | | | | |
| None detected by population sequencing | NR | NR | NR | NR | NR | NR | 70/71 (98.6) | NR |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | NR | NR | NR | NR | NR | NR | 3/3 (100.0) | NR |
| NS5A RAVs with > 5x elevation in EBR $EC_{50}$ | NR | NR | NR | NR | NR | NR | 3/5 (60.0) | NR |
| **GT 1a** | | | | | | | | |
| None detected by population sequencing | NR | NR | NR | NR | NR | NR | 25/26 (96.1%) | NR |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | NR | NR | NR | NR | NR | NR | 3/3 (100%) | NR |
| NS5A RAVs with > 5x elevation in EBR $EC_{50}$ | NR | NR | NR | NR | NR | NR | 0/1 (0.0%) | NR |
| **GT 1b** | | | | | | | | |
| None detected by population sequencing | NR | NR | NR | NR | NR | NR | 45/45 (100.0%) | NR |

| | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | **TN NC GT 1b: EBR/GZR for 12 Weeks (n = 13)** | **TN NC GT 1a: EBR/GZR for 12 Weeks (n = 31)** | **TN NC GT 1b: EBR/GZR for 8 Weeks (n = 31)** | **TN HIV NC GT 1: EBR/GZR for 12 Weeks (n = 30)** | **TN C GT 1: EBR/GZR for 12 Weeks (n = 29)** | **Null responder GT 1: EBR/GZR for 12 Weeks (n = 33)** | **EBR/GZR + RBV for 12 Weeks (n = 79)** | **EBR/GZR for 12 Weeks (n = 19)** |
| NS5A RAVs with ≤ 5x elevation in EBR $EC_{50}$ | NR | NR | NR | NR | NR | NR | 0/0 (NA) | NR |
| NS5A RAVs with > 5x elevation in EBR $EC_{50}$ | NR | NR | NR | NR | NR | NR | 3/4 (75.0%) | NR |
| **Virologic breakthrough (full analysis set) at follow-up week 12** | | | | | | | | |
| GT 1a | NA | 0 | NA | 2/22 (9.1) | 0 | 0 | 0 | NA |
| GT 1b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NA |
| GT 4 | NA | NA | NA | NA | NA | NA | NA | 0 |
| **Relapse (full analysis set) at follow-up week 12** | | | | | | | | |
| GT 1a, n/N (%) | NA | 1/30 (3.3) | NA | 0 | 1/20 (5.0) | 2/22 (9.1) | 2/30 (6.7) | NA |
| GT 1b, n/N (%) | 0 | 0 | 2/31 (6.5) | 0 | | 1/11 (9.1) | 1/49 (2.0) | NA |
| GT 4, n/N (%) | NA | NA | NA | NA | NA | NA | NA | 0 |

C = cirrhotic; CI = confidence interval; DAA = direct-acting antiviral agent; EBR = elbasvir; $EC_{50}$ = effective concentration necessary to inhibit a replicon; GT = genotype; GZR = grazoprevir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NA = not applicable; NR = not reported; NC = non-cirrhotic; NS5A = nonstructural protein 5A; PP = per-population; PR = pegylated interferon plus ribavirin; RAV = resistance-associated variant; RBV = ribavirin; RNA = ribonucleic acid; SVR12 = sustained virologic response 12 weeks after cessation of study medications; TN = treatment-naive.

[a] Only genotype 4 patients included in this cell.

[b] "Other" reasons for failure include administrative reasons and safety and/or tolerability.

Source: Buti et al.;[39] Clinical Study Reports: C-WORTHY;[18] C-SCAPE;[19] C-SALVAGE.[20]

**TABLE 15: SUMMARY OF SF-36 PHYSICAL COMPONENT SCALE AND MENTAL COMPONENT SCALE**

| | Treatment-Naive Patients | | | Mixed Experience | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | C-EDGE Treatment-Experienced[c] | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (n = 111) | PBO 12 Weeks (n = 113) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) |
| **SF-36 PCS[a,b]** | | | | | | | |
| Baseline | | | | | | | |
| n | 314 | 104 | 217 | 109 | 110 | 105 | 104 |
| Mean (SD) | 51.69 (8.44) | 50.64 (8.57) | 50.93 (8.61) | 42.49 (8.61) | 44.30 (8.20) | 50.85 (7.95) | 50.55 (8.14) |
| Week 12 | | | | | | | |
| n | 307 | 103 | 202 | 96 | 96 | 99 | 93[d] |
| Mean (95% CI) change from baseline | –0.11 (–0.83 to 0.62) | 0.50 (–0.60 to 1.61) | 0.89 (–0.07 to 1.86) | 1.18 (–0.18 to 2.55) | –0.52 (–2.29 to 1.25) | 0.52 (–0.82 to 1.86) | –2.35 (–3.96 to –0.75) |
| Treatment difference mean (95% CI) | –0.61 (–2.01 to 0.79) | | NA | 1.71 (–0.51 to 3.93) | | NR | |
| Follow-up week 4 | | | | | | | |
| n | 303 | 102 | NR | NR | NR | NR | NR |
| Mean (95% CI) change from baseline | 0.92 (0.25 to 1.59) | 0.07 (–1.22 to 1.37) | NR | NR | NR | NR | NR |
| Treatment difference mean (95% CI) | 0.85 (–0.53 to 2.22) | | NR | NR | NR | NR | |
| Follow-up week 12 | | | | | | | |
| n | 301 | NR | 172 | 90 | NR | 96 | 91 |
| Mean (95% CI) change from baseline | 0.66 (–0.04 to 1.37) | NR | 1.04 (–0.05 to 2.14) | 0.89 (–3.14 to 4.92) | NR | 1.46 (0.03 to 2.90) | 0.83 (–0.41 to 2.07) |
| Treatment difference mean (95% CI) | NR | | NA | NR | | NR | |
| **SF-36 MCS[a,b]** | | | | | | | |
| Baseline | | | | | | | |
| n | 314 | 104 | 217 | 109 | 110 | 105 | 104 |
| Mean (SD) | 47.90 (10.79) | 50.41 (9.20) | 46.88 (11.73) | 48.44 (10.26) | 48.57 (8.96) | 49.97 (10.0) | 50.83 (9.19) |
| Week 12 | | | | | | | |

| | Treatment-Naive Patients | | | Mixed Experience | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | C-EDGE Treatment-Experienced[c] | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** |
| n | 307 | 103 | 202 | 96 | 96 | 99 | 93[d] |
| Mean (95% CI) change from baseline | 1.28 (0.25 to 2.32) | –1.04 (–2.79 to 0.70) | 1.46 (0.16 to 2.76) | –1.14 (–3.07 to 0.80) | –0.44 (–2.08 to 1.20) | 0.64 (–1.18 to 2.45) | –3.67 (—5.44 to –1.89) |
| Treatment difference mean (95% CI) | 2.33 (0.28 to 4.37) | | NA | –0.69 (–3.21 to 1.82) | | NR | |
| Follow-up week 4 | | | | | | | |
| n | 303 | 102 | NR | NR | NR | NR | NR |
| Mean (95% CI) change from baseline | 1.30 (0.27 to 2.34) | –0.72 (–2.45 to 1.02) | NR | NR | NR | NR | NR |
| Treatment difference mean (95% CI) | 2.02 (–0.02 to 4.06) | | NR | NR | NR | NR | |
| Follow-up week 12 | | | | | | | |
| N | 301 | NR | 172 | 90 | NR | 96 | 91 |
| Mean (95% CI) change from baseline | 1.78 (0.74 to 2.81) | NR | 0.21 (–1.51 to 1.94) | 1.28 (–0.24 to 2.81) | NR | 1.63 (–0.17 to 3.42) | 0.80 (–0.70 to 2.29) |
| Treatment difference mean (95% CI) | NR | | NA | NR | | NR | |
| **Vitality[a]** | | | | | | | |
| Baseline | | | | | | | |
| n | 314 | 104 | 217 | 109 | 110 | 105 | 104 |
| Mean (SD) | 59.87 (22.61) | 60.94 (19.61) | 59.45 (22.28) | 54.19 (21.50) | 57.22 (18.47) | 60.95 (20.36) | 62.80 (22.40) |
| Week 12 | | | | | | | |
| n | 307 | 103 | 202 | 96 | 96 | 99 | 93[d] |
| Mean (95% CI) change from baseline | 2.52 (0.18 to 4.87) | 0.49 (–3.26 to 4.23) | 5.07 (2.48 to 7.67) | 0.07 (–3.80 to 3.93) | –2.96 (–6.66 to 0.74) | 4.42 (0.39 to 8.45) | –8.40 (–12.62 to –4.18) |
| Treatment difference mean (95% CI) | 2.04 (–2.54 to 6.62) | | NA | 3.03 (–2.29 to 8.35) | | NR | |
| Follow-up week 4 | | | | | | | |
| n | 303 | 102 | NR | NR | NR | NR | NR |
| Mean (95% CI) change from | 5.32 | 1.47 | NR | NR | NR | NR | NR |

| | Treatment-Naive Patients | | | Mixed Experience | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | C-EDGE Treatment-Experienced[c] | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** |
| baseline | (3.11 to 7.53) | (–2.22 to 5.16) | | | | | |
| Treatment difference mean (95% CI) | 3.85 (—0.51, 8.21) | | NR | NR | NR | NR | |
| Follow-up week 12 | | | | | | | |
| n | 301 | NR | 172 | 90 | NR | 96 | 91 |
| Mean (95% CI) change from baseline | 6.75 (4.49 to 9.01) | NR | 3.45 (0.28 to 6.63) | 2.64 (–1.60 to 6.87) | NR | 6.77 (2.97 to 10.57) | 6.18 (2.26 to 10.10) |
| Treatment difference mean (95% CI) | NR | | NA | NR | | NR | |
| **General Health[a]** | | | | | | | |
| Baseline | | | | | | | |
| n | 314 | 104 | 217 | 109 | 110 | 105 | 104 |
| Mean (SD) | 66.17 (20.93) | 65.64 (21.18) | 64.91 (22.37) | 47.98 (20.00) | 48.19 (20.51) | 65.16 (21.83) | 65.70 (22.32) |
| Week 12 | | | | | | | |
| n | 307 | 103 | 202 | 96 | 96 | 99 | 93[d] |
| Mean (95% CI) change from baseline | 1.62 (–0.20 to 3.44) | 0.31 (–2.95 to 3.57) | 5.04 (2.91 to 7.18) | 2.70 (–0.19 to 5.58) | –0.85 (–4.25 to 2.54) | 4.78 (1.27 to 8.28) | –0.34 (–3.72 to 3.04) |
| Treatment difference mean (95% CI) | 1.31 (–2.35 to 4.96) | | NA | 3.55 (–0.88 to 7.98) | | NR | |
| Follow-up week 4 | | | | | | | |
| n | 303 | 102 | NR | NR | NR | NR | NR |
| Mean (95% CI) change from baseline | 3.14 (1.27 to 5.01) | –1.80 (–4.78 to 1.17) | NR | NR | NR | NR | NR |
| Treatment difference mean (95% CI) | 4.94 (1.30 to 8.59) | | NR | NR | | NR | |
| Follow-up week 12 | | | | | | | |
| n | 301 | NR | 172 | 90 | NR | 96 | 91 |
| Mean (95% CI) change from baseline | 4.08 (2.27 to 5.88) | NR | 1.70 (–1.05 to 4.46) | 4.54 (1.23 to 7.85) | NR | 5.80 (2.08 to 9.53) | 4.36 (0.98 to 7.75) |
| Treatment difference mean | NR | | NA | NR | | NR | |

| | Treatment-Naive Patients | | | Mixed Experience | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | C-EDGE Treatment-Experienced[c] | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** |
| (95% CI) | | | | | | | |
| **Role Physical[a]** | | | | | | | |
| Baseline | | | | | | | |
| n | 314 | 104 | 217 | 109 | 110 | 105 | 104 |
| Mean (SD) | 78.90 (25.46) | 81.19 (24.84) | 74.91 (27.77) | 55.05 (28.97) | 63.52 (27.44) | 78.39 (26.16) | 78.43 (24.80) |
| Week 12 | | | | | | | |
| n | 307 | 103 | 202 | 9 6 | 9 6 | 99 | 93[d] |
| Mean (95% CI) change from baseline | 1.30 (–1.23 to 3.84) | –0.91 (–4.86 to 3.04) | 1.52 (–1.40 to 4.43) | 2.21 (–2.77 to 7.19) | –1.82 (–7.18 to 3.54) | 1.70 (–3.96 to 7.37) | –10.82 (–15.94 to –5.70) |
| Treatment difference mean (95% CI) | 2.21 (–2.71to 7.14) | | NA | 4.04 (–3.24to 11.31) | | NR | |
| Follow-up week 4 | | | | | | | |
| n | 303 | 102 | NR | NR | NR | NR | NR |
| Mean (95% CI) change from baseline | 2.45 (0.12 to 4.79) | –2.51 (–7.06 to 2.04) | NR | NR | NR | NR | NR |
| Treatment difference mean (95% CI) | 4.97 (0.17to 9.77) | | NR | NR | | NR | |
| Follow-up week 12 | | | | | | | |
| n | 301 | NR | 172 | 9 0 | NR | 96 | 91 |
| Mean (95% CI) change from baseline | 2.55 (0.22 to 4.89) | NR | 2.07 (–1.23 to 5.37) | 4.79 (–0.64 to 10.22) | NR | 5.14 (0.35 to 9.94) | 3.37 (–0.35 to 7.08) |
| Treatment difference mean (95% CI) | NR | | NA | NR | | NR | |
| **Role Emotional[a]** | | | | | | | |
| Baseline | | | | | | | |
| n | 314 | 104 | 217 | 109 | 110 | 105 | 104 |
| Mean (SD) | 80.31 (25.23) | 86.22 (21.02) | 76.73 (27.20) | 70.41 (27.13) | 74.09 (25.70) | 83.25 (23.78) | 84.54 (21.52) |
| Week 12 | | | | | | | |
| n | 307 | 103 | 202 | 96 | 96 | 99 | 93[d] |

| | Treatment-Naive Patients | | | Mixed Experience | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | C-EDGE Treatment-Experienced[c] | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (n = 111)** | **PBO 12 Weeks (n = 113)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** |
| Mean (95% CI) change from baseline | 2.36 (–0.24 to 4.96) | –1.62 (–5.48 to 2.25) | 1.90 (–1.28 to 5.07) | –4.95 (–11.05 to 1.15) | –0.02 (–4.26 to 4.23) | –0.67 (–6.35 to 5.00) | –7.98 (–12.13 to –3.82) |
| Treatment difference mean (95% CI) | 3.98 (–1.02 to 8.98) | | NA | –4.93 (–12.31 to 2.45) | | NR | |
| Follow-up week 4 | | | | | | | |
| n | 303 | 102 | NR | NR | NR | NR | NR |
| Mean (95% CI) change from baseline | 2.06 (–0.58 to 4.71) | –1.23 (–5.17 to 2.72) | NR | NR | NR | NR | NR |
| Treatment difference mean (95% CI) | 3.29 (–1.80 to 8.37) | | NR | NR | | NR | |
| Follow-up Week 12 | | | | | | | |
| n | 301 | NR | 172 | 90 | NR | 96 | 91 |
| Mean (95% CI) change from baseline | 1.94 (0.47 to 4.35) | NR | 1.31 (–2.26 to 4.87) | –1.57 (–7.09 to 3.94) | NR | 4.77 (–0.30 to 9.85) | 0.18 (–3.27 to 3.63) |
| Treatment difference mean (95% CI) | NR | | NA | NR | | NR | |

CI = confidence interval; EBR = elbasvir; GT = genotype; GZR = grazoprevir; MCS = mental component summary; NR = not reported; PBO = placebo; PCS = physical component summary; RBV = ribavirin; SD = standard deviation; SF-36 = Short Form 36-Item Health Survey.

[a] Health Domain Scores, ranging from 0 to 100, with 100 representing the best health status.

[b] PCS and MCS scores were calculated using the individual scores linearly transformed using the population norms to the mean of 50 and a standard deviation of 10. Mean Change from Baseline in PCS and MCS scores: < 0: worst health status, ≥ 0: same or better health status.

[c] In the treatment arms EBR/GZR ± RBV for 12 weeks, the EBR/GZR for 12 weeks group reported better health status than the EBR/GZR + RBV for 12 weeks during treatment at week 12, in role physical, and role emotional domains and the MCS. In the treatment arms EBR/GZR ± RBV for 16 weeks, EBR/GZR for 16 weeks group reported better health status than the EBR/GZR + RBV for 16 weeks during treatment at week 16, in role physical, role emotional, general health, vitality domains and the PCS, and MCS.

[d] At week 16.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-SURFER;[15] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 16: SUMMARY OF EQ-5D VISUAL ANALOGUE SCALE**

| | Treatment-Naive Patients | | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-EDGE Treatment-Experienced[a] | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** |
| **Baseline** | | | | | |
| n | 312 | 104 | 215 | 105 | 101 |
| Mean (SD) | 78.65 (17.66) | 80.06 (14.12) | 76.13 (18.00) | 77.77 (17.51) | 77.39 (16.46) |
| **Week** 12 | | | | | |
| n | 308 | 103 | 201 | 99 | 92[b] |
| Mean (95% CI) change from baseline | 1.92 (0.30 to 3.54) | –0.53 (–2.83 to 1.77) | 3.74 (1.70 to 5.78) | 2.79 (–0.17 to 5.74) | –1.72 (–5.27 to 1.84) |
| Treatment difference mean (95% CI) | 2.45 (–0.65 to 5.55) | | NA | NR | |
| **Follow-up week 4** | | | | | |
| n | 304 | 102 | NR | NR | NR |
| Mean (95% CI) change from baseline | 2.38 (0.58 to 4.18) | –3.04 (–6.04 to –0.04) | NR | NR | NR |
| Treatment difference mean (95% CI) | 5.42 (1.87 to 8.97) | | NA | NR | |
| **Follow-up week 12** | | | | | |
| n | 302 | NR | 1.73 | 96 | 91 |
| Mean (95% CI) change from baseline | 2.83 (1.12 to 4.55) | NR | 2.77 (0.41 to 5.14) | 4.60 (1.53 to 7.68) | 4.65 (1.95 to 7.35) |
| Treatment difference mean (95% CI) | NR | | NA | NR | |

CI = confidence interval; EBR = elbasvir; EQ-5D = EuroQol 5-Dimensions questionnaire; EQ VAS = EuroQol Visual Analogue Scale; GT = genotype; GZR = grazoprevir; NA = not applicable; NR = not reported; RBV = ribavirin.

Note: VAS: range from 0 (worst imaginable health state) to 100 (best imaginable health state). Mean change from baseline in EQ VAS Score: <0: worst health status, ≥0: same or better health status.

[a] In the treatment arms EBR/GZR ± RBV for 12 weeks, the EBR/GZR for 12 weeks group had better mean health status than the EBR/GZR + RBV for 12 weeks during treatment at week 12. In the treatment arms EBR/GZR ± RBV for 16 weeks, there were no treatment differences between EBR/GZR for 16 weeks group and EBR/GZR + RBV for 16 weeks during treatment at week 16.

[b] At week 16.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 17: SUMMARY OF FACIT-F SCALE**

| | Treatment-Naive Patients | | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-EDGE Treatment-Experienced[a] | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) |
| **Baseline** | | | | | |
| n | 312 | 104 | 215 | 105 | 101 |
| Mean (SD) | 40.80 (10.90) | 41.04 (10.06) | 38.82 (11.69) | 40.44 (9.73) | 41.72 (9.58) |
| **Week 12** | | | | | |
| n | 308 | 104 | 199 | 99 | 90[b] |
| Mean (95% CI) change from baseline | 0.41 (–0.62 to 1.45) | 0.22 (–1.54 to 1.98) | 2.31 (1.02 to 3.59) | 1.42 (–0.49 to 3.34) | –4.07 (–5.99 to –2.15) |
| Treatment difference mean (95% CI) | 0.19 (–1.86 to 2.24) | | NA | NR | |
| **Follow-up week 4** | | | | | |
| n | 304 | 103 | NR | NR | NR |
| Mean (95% CI) change from baseline | 1.73 (0.75 to 2.71) | 0.19 (–1.34 to 1.73) | NR | NR | NR |
| Treatment difference mean (95% CI) | 1.54 (–0.37 to 3.44) | | NA | NR | |
| **Follow-up week 12** | | | | | |
| n | 302 | NR | 171 | 96 | 89 |
| Mean (95% CI) change from baseline | 1.74 (0.78 to 2.70) | NR | 1.69 (0.11 to 3.27) | 3.60 (2.04 to 5.17) | 0.87 (–0.57 to 2.30) |
| Treatment difference mean (95% CI) | NR | | NA | NR | |

EBR = elbasvir; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; EBR = elbasvir; GT = genotype; GZR = grazoprevir; NA = not applicable; NR = not reported; PBO = placebo; RBV = ribavirin.

Note: Fatigue Scale Score ranges from 0 to 52, higher the score the better quality of life. Mean Change from Baseline in Fatigue Scale Score: <0: worst health status, ≥0: same or better health status.

[a] In the treatment arms EBR/GZR ± RBV for 12 weeks, treatment differences were seen at treatment week 12, showing less fatigue in the GZR/RBV arm as compared to the EBR/GZR + RBV arm for treatment duration of 12 weeks. Similarly In the treatment arms EBR/GZR ± RBV for 16 weeks, treatment differences were seen at treatment week 16, showing less fatigue in the GZR/RBV arm as compared to the EBR/GZR + RBV arm for treatment duration of 16 weeks.

[b] At week 16.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 18: SUMMARY OF OVERALL CLDQ-HCV SCORE**

| | Treatment-Naive Patients | | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-EDGE Treatment-Experienced[a] | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) |
| **Baseline** | | | | | |
| n | 135 | 55 | 82 | 52 | 41 |
| Mean (SD) | 5.22 (1.29) | 5.35 (1.10) | 5.00 (1.36) | 5.46 (1.06) | 5.51 (1.11) |
| **Week 12** | | | | | |
| n | 130 | 55 | 74 | 51 | 37[b] |
| Mean (95% CI) change from baseline | 0.30 (0.15 to 0.44) | 0.28 (0.10 to 0.46) | 0.63 (0.39 to 0.87) | 0.24 (–0.01 to 0.48) | –0.12 (–0.40 to 0.15) |
| Treatment difference mean (95% CI) | 0.02 (–0.23 to 0.26) | | NA | NR | |
| **Follow-up week 4** | | | | | |
| n | 129 | 54 | NR | NR | NR |
| Mean (95% CI) change from baseline | 0.38 (0.23 to 0.52) | 0.25 (0.07 to 0.44) | NR | NR | NR |
| Treatment difference mean (95% CI) | 0.12 (–0.13 to 0.37) | | NA | NR | |
| **Follow-up week 12** | | | | | |
| n | 126 | NR | 67 | 49 | 37 |
| Mean (95% CI) change from baseline | 0.53 (0.37 to 0.69) | NR | 0.69 (0.41 to 0.98) | 0.47 (0.25 to 0.68) | 0.34 (0.07 to 0.61) |
| Treatment difference mean (95% CI) | NR | | NA | NR | |

CLDQ-HCV = HCV-specific version of the Chronic Liver Disease Questionnaire; EBR = elbasvir; GT = genotype; GZR = grazoprevir; NA = not applicable; NR = not reported; RBV = ribavirin.

Note: Scores range from 1 to 7, with 7 representing best quality of life. mean change from baseline in CLDQ Overall Scores: < 0: worst health status, ≥ 0: same or better health status. Only at sites in the US, patients whose native language is either English or Spanish were eligible to complete CLDQ-HCV.

[a] In the treatment arms EBR/GZR ± RBV for 12 weeks, there were no differences in mean change in Overall CLDQ-HCV score at treatment week 12 between EBR/GZR for 12 weeks group and EBR/GZR + RBV for 12 weeks. In the 16 week treatment arms, EBR/GZR group had better health than EBR/GZR + RBV in Overall CLDQ-HCV score at treatment week 16.

[b] At week 16.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 19: SUMMARY OF OVERALL WPAI SCORE**

| | Treatment-Naive Patients | | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-EDGE Treatment-Experienced[a] | |
| | EBR/GZR for 12 Weeks (n = 316) | PBO 12 Weeks (n = 105) | EBR/GZR for 12 Weeks (n = 218) | EBR/GZR for 12 Weeks (n = 105) | EBR/GZR + RBV for 16 Weeks (n = 106) |
| **Per cent impairment while working due to hepatitis C** | | | | | |
| **Baseline** | | | | | |
| N | 182 | 61 | 113 | 59 | 54 |
| Mean (SD) | 10.49 (18.18) | 10.82 (17.92) | 9.82 (20.04) | 8.64 (16.76) | 8.15 (16.38) |
| **Week 12** | | | | | |
| N | 178 | 55 | 109 | 57 | 48[b] |
| Mean (95% CI) change from baseline | 0.44 (–2.21 to 3.10) | 4.00 (–0.49 to 8.49) | –1.14 (–5.10 to 2.83) | –1.14 (–4.60 to 2.32) | 11.25 (4.35 to 18.15) |
| Treatment difference mean (95% CI) | –3.56 (–8.92 to 1.81) | | NA | NR | |
| **Follow-up week 4** | | | | | |
| N | 178 | 54 | NR | NR | NR |
| Mean (95% CI) change from baseline | –1.23 (–3.83 to 1.37) | 0.93 (–2.48 to 4.33) | NR | NR | NR |
| Treatment difference mean (95% CI) | –2.16 (–7.22 to 2.91) | | NA | NR | |
| **Follow-up week 12** | | | | | |
| N | 179 | NR | 90 | 54 | 48 |
| Mean (95% CI) change from baseline | –2.74 (–4.96 to –0.51) | NR | –3.74 (–8.77 to 1.28) | –6.50 (–10.97 to –2.03) | –1.46 (–7.77 to 4.85) |
| Treatment difference mean (95% CI) | NR | | NA | NR | |
| **Per cent activity impairment due to hepatitis C** | | | | | |
| **Baseline** | | | | | |
| N | 311 | 104 | 215 | 105 | 101 |
| Mean (SD) | 18.10 (24.95) | 16.83 (22.95) | 20.60 (28.71) | 15.43 (22.10) | 14.46 (22.69) |
| **Week 12** | | | | | |
| N | 308 | 104 | 201 | 99 | 92[c] |
| Mean (95% CI) change from baseline | –1.30 (–3.65 to 1.05) | –0.96 (–4.26 to 2.34) | –6.47 (–10.19 to –2.74) | –2.73 (–7.12, 1.67) | 10.98 (5.54, 16.42) |
| Treatment difference mean (95% CI) | –0.34 (–4.80 to 4.13) | | NA | NR | |

| | Treatment-Naive Patients | | | Treatment-Experienced Patients | |
|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-EDGE Treatment-Experienced[a] | |
| | **EBR/GZR for 12 Weeks (n = 316)** | **PBO 12 Weeks (n = 105)** | **EBR/GZR for 12 Weeks (n = 218)** | **EBR/GZR for 12 Weeks (n = 105)** | **EBR/GZR + RBV for 16 Weeks (n = 106)** |
| **Follow-up week 4** | | | | | |
| N | 304 | 103 | NR | NR | NR |
| Mean (95% CI) change from baseline | –4.34 (–6.82 to –1.87) | –1.07 (–4.74 to 2.60) | NR | NR | NR |
| Treatment difference mean (95% CI) | –3.27 (–8.02 to 1.47) | | NA | NR | |
| **Follow-up week 12** | | | | | |
| N | 302 | NR | 173 | 96 | 91 |
| Mean (95% CI) change from baseline | –6.36 (–8.78 to –3.94) | NR | –9.71 (–13.88 to –5.54) | –6.56 (–11.26 to –1.86) | –1.21 (–6.18 to 3.77) |
| Treatment difference mean (95% CI) | NR | NR | NA | NR | |

EBR = elbasvir; GT = genotype; GZR = grazoprevir; NA = not applicable; NR = not reported; PBO = placebo; RBV = ribavirin; WPAI = Work Productivity and Activity Impairment questionnaire.

Note: Mean change from baseline in impairment scores: < 0: less impairment, ≥ 0: same or greater impairment.

[a] There were no differences in mean change scores from baseline in impairment domain between EBR/GZR and EBR/GZR + RBV for 12 weeks of therapy. For 16 weeks of treatment, treatment differences were seen, where patients treated with EBR/GZR for 16 weeks had less activity impairment than EBR/GZR + RBV at treatment week 16.

[b] At week 16.

Source: Clinical Study Reports: C-Edge Treatment-Experienced;[13] C-Edge Treatment-Naive;[16] C-EDGE Coinfection.[17]

**TABLE 20: ADVERSE EVENTS**

| Common AE[a] | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks | PBO 12 Weeks | EBR/GZR for 12 Weeks | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) | EBR/GZR for 12 Weeks | PBO 12 Weeks | EBR/GZR for 12 Weeks | EBR/GZR + RBV for 16 Weeks | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) |
| Diarrhea | 14 (4.4) | 7 (6.7) | 17 (7.8) | 1 (9.1) | 6 (5.4) | 15 (13.3) | 5 (4.8) | 9 (8.5) | 0 | 1 (8.3) |
| Nausea | 28 (8.9) | 8 (7.6) | 20 (9.2) | 1 (9.1) | 17 (15.3) | 18 (15.9) | 9 (8.6) | 18 (17.0) | 1 (7.1) | 1 (8.3) |
| Fatigue | 49 (15.5) | 18 (17.1) | 29 (13.3) | 2 (1 8.2) | 11 (9.9) | 17 (15.0) | 20 (19.0) | 32 (30.2) | 0 | 1 (8.3) |
| Nasopharyngitis | 14 (4.4) | 6 (5.7) | 11 (5.0) | 1 (9.1) | 3 (2.7) | 5 (4.4) | 3 (2.9) | 3 (2.8) | 0 | 0 |
| Arthralgia | 20 (6.3) | 6 (5.7) | 10 (4.6) | 0 | 4 (3.6) | 4 (3.5) | 4 (3.8) | 3 (2.8) | 0 | 0 |
| Dizziness | 9 (2.8) | 7 (6.7) | 8 (3.7) | 2 (1 8.2) | 6 (5.4) | 18 (15.9) | 6 (5.7) | 6 (5.7) | 0 | 0 |
| Headache | 52 (16.5) | 19 (18.1) | 27 (12.4) | 4 (3 6.4) | 19 (17.1) | 19 (16.8) | 22 (21.0) | 20 (18.9) | 0 | 1 (8.3) |
| Insomnia | 4 (1.3) | 6 (5.7) | 15 (6.9) | 3 (2 7.3) | 7 (6.3) | 12 (10.6) | 5 (4.8) | 10 (9.4) | NR | NR |
| Pruritus | 7 (2.2) | 8 (7.6) | 5 (2.3) | 0 | 4 (3.6) | 11 (9.7) | 1 (1.0) | 11 (10.4) | 1 (7.1) | 0 |
| Upper respiratory tract infection | 1 3 (4.1) | 1 (1.0) | 17 (7.8) | 0 | 1 (0.9) | 2 (1.8) | 3 (2.9) | 5 (4.7) | 0 | 0 |
| Decreased appetite | 1 0 (3.2) | 2 (1.9) | 5 (2.3) | 1 (9.1) | 6 (5.4) | 3 (2.7) | 2 (1.9) | 6 (5.7) | NR | NR |
| Musculoskeletal pain | 2 (0.6) | 4 (3.8) | 4 (1.8) | 0 | 0 | 6 (5.3) | 2 (1.9) | 0 | NR | NR |
| Myalgia | 8 (2.5) | 3 (2.9) | 5 (2.3) | 0 | 0 | 8 (7.1) | 2 (1.9) | 7 (6.6) | 0 | 0 |
| Cough | 9 (2.8) | 4 (3.8) | 2 (0.9) | 0 | 8 (7.2) | 2 (1.8) | 6 (5.7) | 9 (8.5) | 0 | 0 |
| Hypertension | 4 (1.3) | 1 (1.0) | 4 (1.8) | 1 (9.1) | 7 (6.3) | 7 (6.2) | 4 (3.8) | 0 | NR | NR |
| Abdominal discomfort | 1 (0.3) | 2 (1.9) | 1 (0.5) | 1 (9.1) | 1 (0.9) | 6 (5.3) | 0 | 1 (0.9) | 0 | 0 |
| Abdominal pain | 1 3 (4.1) | 3 (2.9) | 3 (1.4) | 0 | 10 (9.0) | 3 (2.7) | 5 (4.8) | 3 (2.8) | NR | NR |
| Constipation | 1 2 (3.8) | 3 (2.9) | 9 (4.1) | 1 (9.1) | 6 (5.4) | 6 (5.3) | 1 (1.0) | 5 (4.7) | 0 | 0 |
| Vomiting | 9 (2.8) | 0 | 7 (3.2) | 1 (9.1) | 8 (7.2) | 7 (6.2) | 2 (1.90) | 9 (8.5) | 0 | 1 (8.3) |

| Common AE[a] | Treatment-Naive Patients | | | Mixed Experience | | | Treatment-Experienced Patients | | Treatment-Naive Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-EDGE Treatment-Naive | | C-EDGE Coinfection | C-SURFER | | | C-EDGE Treatment-Experienced | | C-SWIFT | |
| | EBR/GZR for 12 Weeks | PBO 12 Weeks | EBR/GZR for 12 Weeks | EBR/GZR for 12 Weeks (Not Randomized [PK Arm]) | EBR/GZR for 12 Weeks | PBO 12 Weeks | EBR/GZR for 12 Weeks | EBR/GZR + RBV for 16 Weeks | EBR/GZR + SOF for 12 Weeks (Non-cirrhotic Patients) | EBR/GZR + SOF for 12 Weeks (Cirrhotic Patients) |
| Asthenia | 9 (2.8) | 2 (1.9) | 9 (4.1) | 0 | 6 (5.4) | 5 (4.4) | 7 (6.7) | 10 (9.4) | NR | NR |
| Pyrexia | 3 (0.9) | 0 | 5 (2.3) | 0 | 6 (5.4) | 6 (5.3) | 3 (2.9) | 2 (1.9) | NR | NR |
| Accidental overdose | 5 (1.6) | 2 (1.9) | 8 (3.7) | 0 (0.0) | 4 (3.6) | 3 (2.7) | 3 (2.9) | 14 (13.2) | 1 (7.1) | 0 |
| Dyspepsia | 2 (0.6) | 1 (1.0) | 2 (0.9) | 1 (9.1) | 2 (1.8) | 4 (3.5) | 3 (2.9) | 7 (6.6) | 0 | 0 |
| Irritability | 9 (2.8) | 4 (3.8) | 2 (0.9) | 0 | 1 (0.9) | 0 | 4 (3.8) | 8 (7.5) | 0 | 0 |
| Rash | 6 (1.9) | 1 (1.0) | 4 (1.8) | 0 | 2 (1.8) | 3 (2.7) | 2 (1.9) | 8 (7.5) | 0 | 0 |
| Vertigo | 7 (2.2) | 1 (1.0) | NR | 0 | 2 (1.8) | 2 (1.8) | 2 (1.9) | 0 | 1 (7.1) | 0 |
| Dyspnea | NR | NR | NR | NR | NR | NR | 1 (1.0) | 10 (9.4) | NR | NR |
| Dyspnea exertional | NR | NR | NR | NR | NR | NR | 1 (1.0) | 8 (7.5) | NR | NR |
| Dysgeusia | 1 (0.3) | 3 (2.9) | 1 (0.5) | 0 | 1 (0.9) | 4 (3.5) | 1 (1.0) | 3 (2.8) | 1 (7.1) | 0 |

AE = adverse event; EBR = elbasvir; GT = genotype; GZR = grazoprevir; NA = not applicable; NR = not reported; PBO = placebo; PK = pharmacokinetic; RBV = ribavirin; SOF = sofosbuvir.

[a] Frequency > 5%.

**TABLE 20: ADVERSE EVENTS, CONTINUED**

| Common AE[a] | C-WORTHY | | | | | | C-SALVAGE | C-SCAPE |
|---|---|---|---|---|---|---|---|---|
| | TN NC GT1b: EBR/GZR for 12 Weeks | TN NC GT1a: EBR/GZR for 12 Weeks | TN NC GT1b: EBR/GZR for 8 Weeks | TN HIV NC GT1: EBR/GZR for 12 Weeks | TN C GT1: EBR/GZR for 12 Weeks | NR GT1: EBR/GZR for 12 Weeks | EBR/GZR + RBV for 12 Weeks | EBR/GZR for 12 Weeks |
| Diarrhea | 1 (8.3) | 4 (12.9) | 2 (6.5) | 0 | 1 (3.4) | 0 | 6 (7.6) | 3 (15.8) |
| Nausea | 2 (16.7) | 5 (16.1) | 3 (9.7) | 1 (3.3) | 0 | 2 (6.1) | 9 (11.4) | 1 (5.3) |
| Fatigue | 4 (33.3) | 6 (19.4) | 3 (9.7) | 2 (6.7) | 6 (20.7) | 10 (30.3) | 22 (27.8) | 2 (10.5) |
| Headache | 5 (41.7) | 10 (32.3) | 5 (16.1) | 2 (6.7) | 4 (13.8) | 6 (18.2) | 15 (19.0) | 1 (5.3) |
| Myalgia | 2 (16.7) | 1 (3.2) | 3 (9.7) | 0 | 1 (3.4) | 6 (18.2) | 3 (3.8) | 1 (5.3) |
| Cough | 0 | 0 | 0 | 1 (3.3) | 2 (6.9) | 1 ( 3 . 0 ) | 2 (2.5) | 2 (10.5) |
| Asthenia | 0 | 3 (9.7) | 1 (3.2) | 1 (3.3) | 1 (3.4) | 5 (15.2) | 12 (15.2) | 4 (21.1) |
| Depression | 2 (16.7) | 1 (3.2) | 1 (3.2) | 0 | 0 | 0 | 2 (2.5) | 1 (5.3) |

AE = adverse event; C = cirrhotic; EBR = elbasvir; GT = genotype; GZR = grazoprevir; NA = not applicable; NC = non-cirrhotic; NR = not reported; PBO = placebo; PK = pharmacokinetic; RBV = ribavirin; TN = treatment-naive.

[a] Frequency > 10%.

# APPENDIX 5: VALIDITY OF OUTCOME MEASURES

## Aim

To summarize the validity of the following outcome measures:

- Sustained virologic response at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24)
- EuroQol 5 Dimensions questionnaire (EQ-5D)
- Short Form 36-Item Health Survey (SF-36)
- Chronic Liver Disease Questionnaire–Hepatitis C (CLDQ-HCV)
- Functional Assessment of Chronic Illness–Fatigue (FACIT-F)
- Work Productivity and Activity Impairment–Hepatitis C (WPAI-HepC).

## Findings

The above outcome measures are briefly summarized in Table 21.

**TABLE 21: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES**

| Instrument | Type | Evidence of Validity | MCID | References |
|---|---|---|---|---|
| SVR12 and 24 | SVR at week 12 and 24 are end points for assessing response to drugs that treat CHC infection. | Yes | Not applicable | Chen et al.[62] |
| EQ-5D | EQ-5D is a general, non–disease-specific HRQoL questionnaire. | No | Unknown | EuroQol group[63] |
| SF-36 | SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. | Yes | 2 to 4 | Ware et al.[47] |
| CLDQ-HCV | The CLDQ is an HRQoL instrument for patients with chronic liver disease. | Yes | 0.5 | Younossi et al.[64] |
| FACIT-F | FACIT-F is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, energy, and the impact of fatigue on daily activities and function. | No | Unknown | CSR[16] |
| WPAI-HepC | WPAI is an instrument used to measure the impact of a disease on work and on daily activities. | No | Unknown | Reilly et al.[65] |

CHC = chronic hepatitis C; CLDQ-HCV= Chronic Liver Disease Questionnaire – Hepatitis C; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; FACIT-F = Functional Assessment of Chronic Illness–Fatigue; HRQoL = health-related quality of life; MCID = minimal clinically important difference; SF-36= Short Form 36-item instrument; SVR12 and 24 = sustained virologic response at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24); WPAI-HepC = Work Productivity and Activity Impairment–Hepatitis C

### SVR12 and 24

SVR24 is the standard primary end point for assessing response to drugs that treat chronic hepatitis C (CHC) infection.[62] However, SVR12 is an emerging outcome of interest, potentially providing a means for determining treatment response earlier in either randomized controlled trials or the clinic. In 2013, the FDA published a paper that sought to determine the predictive value of SVR12 as a surrogate for SVR24.[62] The authors reviewed data submitted to the FDA (2002-2011) from 15 phase 2 and 3 studies that included various treatment durations of pegylated interferon alfa-2a, pegylated interferonalfa-2b, albinterferon alfa-2b, telaprevir, and boceprevir. The majority of the 13,599 participants were genotype 1

(N = 11,730), while 69 patients had genotype 4. In addition to assessing SVR12, the authors also reviewed the predictive value of SVR4 with respect to SVR24.

SVR12 was achieved by 51.8% (7,051 of 13,599 patients) and SVR24 by 50.6% (6,881 of 13,599 patients) of adults in the database.[62] The positive predictive value between SVR12 and SVR24 was 98.3% and the negative predictive value was 98.8%. Thus, 1.2% of patients would be falsely identified as not achieving SVR if an outcome of SVR12 was adopted over SVR24, and 1.7% of patients would be falsely identified as having a sustained undetectable viral load. The authors attributed the latter to relapse, reinfection, or "other" reasons. Results were consistent across the 15 studies, with between 0% and 4.3% of patients achieving SVR12 but not SVR24. Older studies that used hepatitis C (HCV) ribonucleic acid (RNA) assays with higher values for lower limits of detection had lower positive predictive values than those studies with newer, more sensitive assays. Overall, the authors concluded that SVR12 would be an appropriate primary end point for trials used by regulatory bodies to evaluate CHC treatments.[62] They also stated that these conclusions should be applied with caution to direct-acting antiviral agent (DAA)–only regimens, considering that they were based on data from regimens containing interferon plus ribavirin.[62] Further monitoring of interferon-free clinical trials may be required to determine the appropriate end point.

A study published in 2010 also evaluated the relevance of SVR12 as a primary outcome.[66] This study included 781 patients with CHC; all had received PR. Among the 781 individuals, 74 patients had genotype 4 or 5 CHC (genotype 4 was not reported separately from genotype 5). Of the 781 patients, 573 had an end-of-treatment response and were thus included in the analysis. Of the 409 patients who had an SVR12, 408 went on to have an SVR24.[66] Therefore, this study also demonstrated a high concordance between achievement of SVR12 and eventual achievement of SVR24. The authors concluded that SVR12 is as informative as SVR24 when assessing SVR. This study used the transcription-mediated amplification assay, which is a newer, more sensitive assay.

Another study explored differences between SVR12 and SVR24 among treatment-naive genotype 1 CHC patients who received pegylated interferon plus ribavirin (PR).[67] The authors pooled single-arm data for pegylated interferon alfa 2a or alfa 2b plus ribavirin from 35 clinical trials. Of these trials, only one study reported both SVR12 and SVR24. The proportion with an SVR12 or SVR24 was pooled across trials using a DerSimonian–Laird random effects model. Data for SVR12, SVR24 and for each type of pegylated interferon were pooled separately. The authors also performed a Bayesian random effects meta-regression of the proportion with SVR12 or SVR24, controlling for the type of pegylated interferon. The authors concluded that SVR12 was 5% to 6% higher than SVR24 although the credible intervals overlapped in the conventional meta-analysis, and in the Bayesian meta-regression the credible intervals included the null value (SVR12 versus SVR24 relative risk 1.13; 95% credible interval, 0.99 to 1.26).[67] These findings should be interpreted with caution, considering that they were based on single treatment group data. Naive pooling of single-arm data is not an acceptable method to determine comparative efficacy as it ignores the benefits of randomization and may therefore be subject to the same biases as a comparison of independent cohort studies. In addition, the analysis was limited to data from patients who received PR, and did not examine the concordance of SVR12 and SVR24 among those who received a DAA regimen.

One study performed an analysis of the concordance between SVR12 and SVR24 using pooled data from phase 3 clinical trials of sofosbuvir-containing regimens (NEUTRINO, FISSION, POSITRON, FUSION, and VALENCE).[68] From this analysis, a total of 777 of 779 patients (99.7%) who achieved SVR12 also achieved SVR24, including all patients (n = 296) with hepatocellular carcinoma (HCC) genotype 1 or 4 to 6, all

patients (n = 270) with genotype 2, and 211 or 213 patients (99.0%) with genotype 3. Thus the negative predictive value measuring concordance between SVR12 and SVR24 was 100% and positive predictive value was 99.7%.

**EQ-5D**

The EuroQol 5-Dimensions Quality of Life Scale (EQ-5D) is a generic health-related quality of life (HRQoL) instrument that may be applied to a wide range of health conditions and treatments.[63,69] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged 12 years or older), based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions, corresponding with 243 different health states. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[63,69] The second part is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for the 3L version (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported minimal clinically important differences (MCIDs) for the 3L version of the scale have ranged from 0.033 to 0.074.[70]

The investigators of the included study in this review used the EQ-5D-5L version. This version of the descriptive system consists of the same five dimensions as the standard version (EQ-5D-3L), but includes five response levels instead of three: no problems, slight problems, moderate problems, severe problems, and unable to do/extreme problems for all dimensions.[71] There are 3,125 possible health states associated with the 5L version of the EQ-5D.

The validity of the 5L version was compared with the standard version among patients with chronic hepatic diseases (n = 1,088), among whom 31.8% had CHC.[71] Overall, in comparison with the standard version, the 5L version appeared to be more feasible (0.8% vs. 8.5% of patients returned blank questionnaires). The overall proportion of inconsistent responses between the two versions was 2.9%, similar to the minimum possible value (1.12%). The proportion of respondents answering "11111" was 39.4% with the standard version and 36.4% with the 5L system, indicating an absolute reduction of 2.9% and a relative reduction of 7.5% of the ceiling effect on the full profile. The correlation coefficient between 5L and VAS was moderate to high, ranging from –0.39 for self-care to a maximum of –0.55 for usual activities. There were no relevant differences in correlations between individual dimensions and

the VAS between the standard and 5L versions. Other psychometric properties such as responsiveness and reliability were not assessed. The MCID for the EQ-5D-5L among CHC patients was not assessed.

**Short Form 36-Item Health Survey**

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. SF-36 consists of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 also provides two component summaries: the physical component summary (SF-36 PCS) and the mental component summary (SF-36 MCS), which are created by aggregating the eight domains. The SF-36 PCS, SF-36-MCS, and eight domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of SF-36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient.[47]

A systematic review was conducted to identify and provide information on HRQoL instruments for hepatitis C.[46] The authors identified 32 studies and presented the results by types of clinical anchors (for example, hepatitis C status or liver disease severity anchors), but it was not clear in the publication which instruments contributed to the data. Nonetheless, from the publication, two results attributed to SF-36 could be extracted:

- A total of 15 studies with SF-36 were included that compared HRQoL in patients with compensated hepatitis C seropositivity versus healthy controls. All 15 studies provided cross-sectional group mean HRQoL differences stratified by hepatitis C status (the clinical anchor). Patients with hepatitis C scored lower on the various domains compared with healthy patients. The largest impact of the disease was on role physical, role emotional, and general health (Table 22).[46]
- A panel of experts was convened to indirectly estimate the MCID in hepatitis C based upon existing HRQoL data.[46] The panel consisted of three hepatologists and two HRQoL methodologists with expertise in chronic liver disease–specific HRQoL. Based on the results of the systematic review, the panel determined that the SF-36 vitality scale captures the HRQoL domain that is most relevant to patients with hepatitis C. Using a modified Delphi technique, the expert panel generated a mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale, with a corresponding effect size of 0.2 (range 0.15 to 0.25).[46] MCIDs for other dimensions or for the two component scores were not estimated. Of note, this study did not use an anchor-based method, which may be preferred, to generate the MCID and, as such, it is unclear if the estimates represent values patients would identify as clinically important.[72]

No MCID estimates in patients with CHC were found for the component scores or for domains other than vitality. It is unclear if the MCID estimates from other conditions or the general population are generalizable to HCV.

**TABLE 22: HEPATITIS C PATIENT VERSUS HEALTHY CONTROL WEIGHTED MEAN AND MEDIAN CROSS-SECTIONAL DIFFERENCE (15 STUDIES)**

| Scale | Weighted Mean | Median |
|---|---|---|
| Physical function | −7.0 | −9.3 |
| Role physical | −15.8 | −20.5 |
| Bodily pain | −9.0 | −13.7 |
| General health | −12.6 | −19.6 |
| Vitality | −10.1 | −14.4 |

| Scale | Weighted Mean | Median |
|---|---|---|
| Social function | −11.9 | −10.0 |
| Role emotional | −13.0 | −12.5 |
| Mental health | −7.2 | −10.0 |
| Mental component score | −12.8 | −7.0 |
| Physical component score | −9.1 | −6.6 |

**Chronic Liver Disease Questionnaire — Hepatitis C**

The CLDQ is an HRQoL instrument for patients with chronic liver disease. The CLDQ includes 29 items divided into six domains: Abdominal Symptoms, Fatigue, Systemic Symptoms, Activity, Emotional Function, and Worry. For each item, the patient assigns a score of 1 (all the time) to 7 (none of the time). The domain score is the sum of the item scores for that domain, divided by the number of items in that respective domain. The overall CLDQ score is the mean of the domain scores. Scores are presented on a 1 to 7 scale, with higher numbers indicating the best possible function.[64] In the paper by Younossi et al.,[64] the investigators stated that a change of 0.5 on the 1 to 7 scale would signify an important difference in questionnaire score; however, there is no proof of validation of this MCID.[72]

It appears that the CLDQ was subsequently amended for use in CHC patients. From abstracts, we could find that scores are based on a Likert scale from 0 (worst) to 7 (best) and measure Activity/Energy, Emotion, Worry, Systemic, and CLDQ-HCV total score.[73,74] No detailed information was available.

An MCID for CLDQ-HCV has not been estimated, although one abstract[74] cited an MCID of 0.5, perhaps in reference to the paper by Younossi et al.[64] mentioned above.

Three abstracts on convergent validity and one abstract on construct validity of CLDQ-HCV were identified.[73-76]

**Convergent Validity**

CLDQ-HCV was validated against the Fatigue Severity Scale (high score = more fatigue) in 100 consecutive healthy blood donors and from 50 CHC patients.[75] Correlations between Fatigue Severity Scale and CLDQ-HCV in the 100 healthy blood donors were as follows: Activity/ Energy, $r = –0.65$ ($P = 0.0001$); Emotion, $r = –0.61$ ($P < 0.0001$); Worry, $r = –0.23$ ($P < 0.0001$); Systemic, $r = –0.39$ ($P < 0.0001$); and Overall Score, $r = 0.58$ ($P < 0.0001$). Comparison of CLDQ-HCV scores between blood donor patients and CHC patients showed statistically significant differences in HRQoL measured by Worry ($P < 0.0001$), Emotion ($P = 0.048$), and Overall Score ($P = 0.004$), with worse (lower) scores in CHC patients.[75]

CLDQ-HCV was validated against SF-36 in 50 hepatitis C patients. CLDQ-HCV Activity/Energy (A/E) domain and SF-36 vitality (VT) and physical functioning (PF) scales were used. Statistically significant correlations were shown (VT versus A/E, $r = 0.84$ ($P < 0.0001$); VT versus PF, $r = 0.48$, $P < 0.0001$)].[76]

In another abstract, CLDQ-HCV was validated against SF-36 in 63 hepatitis C patients. The following r values were obtained (Table 23).[73] All findings were statistically significant.

**TABLE 23: CORRELATION BETWEEN VARIOUS DOMAINS OF CLDQ-HCV AND SF-36**

| *r* Value (*P* Value) | CLDQ-HCV | | | | |
|---|---|---|---|---|---|
| SF-36 | Activity/Energy | Emotion | Worry | Systemic | Overall Score |
| Physical function | 0.47 (< 0.001) | NR | NR | 0.40 (0.006) | NR |
| Role physical | 0.42 (0.001) | NR | NR | NR | NR |
| Bodily pain | 0.47 (< 0.001) | NR | NR | 0.53 (< 0.001) | 0.41 (0.002) |
| General health | 0.40 (0.003) | 0.44 (0.001) | NR | 0.44 (0.001) | 0.41 (0.003) |
| Vitality | 0.78 (0.001) | 0.41 (0.003) | NR | 0.46 (0.001) | 0.57(< 0.001) |
| Social function | 0.43 (0.001) | NR | NR | NR | NR |
| Role emotional | NR | NR | NR | NR | NR |
| Mental health | NR | 0.58 (< 0.001) | NR | NR | NR |
| Mental component score | 0.49 (0.001) | 0.59 (< 0.001) | NR | 0.40 (0.01) | 0.49 (< 0.001) |
| Physical component score | 0.68 (< 0.001) | NR | NR | 0.52 (< 0.001) | 0.44 (0.002) |

CLDQ-HCV = Chronic Liver Disease Questionnaire—Hepatitis C Virus; NR = not reported; SF-36 = Short Form 36-Item Health Survey.
Source: Escheik et al.[73]

**Construct Validity**

One abstract presented data on the validation of CLDQ-HCV in 62 hepatitis C patients versus 100 healthy blood donors.[74] Hepatitis C patients received PR treatment. Hepatitis C patients had lower (worse) CLDQ-HCV Overall Score at baseline compared with healthy controls (5.7 ± 0.7 versus 6.2 ± 0.5, $P < 0.0001$). Lower scores were also reported at baseline for Emotion and Worry in hepatitis C patients (5.6 ± 0.4 and 5.7 ± 0.9) compared with healthy controls (5.9 ± 0.4 and 6.9 ± 0.2), respectively. After four weeks and 24 weeks of treatment, Overall Scores decreased (worsened) in hepatitis C patients (5.4 ± 0.9 and 5.7 ± 0.8), and increased after treatment discontinuation (6.3 ± 0.6). The CLDQ-HCV was able to differentiate between hepatitis C patients and healthy controls. The instrument was also sensitive to change over time.[74]

**Functional Assessment of Chronic Illness Therapy — Fatigue**

The Functional Assessment of Cancer Therapy (FACT) was originally developed and validated in cancer patients.[77] The Functional Assessment of Chronic Illness Therapy (FACIT) was later derived from FACT and validated in patients with chronic conditions such as multiple sclerosis and rheumatoid arthritis.[42] The FACIT measurement system is based on a generic core questionnaire (FACT-General), which includes 27 items divided into four primary domains: physical, social/family, emotional, and functional well-being.[42] The Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-F) is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, energy as well as fatigue's impact on daily activities and function, and includes an additional 13 items scored using a 5-point Likert-type response scale to rate each item, where 0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much with a recall period of "during the past seven days." [16] Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale (40 items in total), make up the total score, ranging from 0 (worst) to 160 (best).[41] Although no information on the validity of FACIT-F or its MCID in hepatitis C patients was found, the MCID for the FACT-General total score ranged from 3 to 7 points in cancer patients, and the MCID in the FACIT-F ranged from 3 to 4 points in rheumatoid arthritis patients.[42,43]

**Work Productivity and Activity Impairment — Hepatitis C**

The Work Productivity and Activity Impairment (WPAI) questionnaire is an instrument used to measure the impact of a disease on work and on daily activities and consists of six questions: Q1 = currently employed; Q2 = hours missed due to health problems; Q3 = hours missed other reasons; Q4 = hours actually worked; Q5 = degree health affected productivity while working (using a 0 to 10 VAS); Q6 = degree health affected productivity in regular unpaid activities (VAS).[44,45,65] The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (work impairment) during the past seven days. The work impairment domain is the sum of impairment in work productivity due to absenteeism (productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days) and impairment due to decreased productivity while at work (reduced performance of productivity while at work due to health reasons, including time not being on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. Four main outcomes can be generated from the WPAI and expressed in percentages by multiplying the following scores by 100: 1) per cent work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed; 2) per cent impairment while working due to health = Q5/10 for those who were currently employed and actually worked in the past seven days; 3) per cent overall work impairment due to health = Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) × (Q5/10)) for those who were currently employed; 4) per cent activity impairment due to health = Q6/10 for all respondents. For those who missed work and did not actually work in the past seven days, the per cent overall work impairment due to health will be equal to the per cent work time missed due to health. The scores are presented as a percentage with lower values indicating better quality of life.[44,45]

One study, available only as an abstract, measured the content validity of WPAI in hepatitis C using cognitive debriefing interviews. A total of seven patients interviewed confirmed that the questionnaire was relevant, understandable, and easy to complete.[78]

Although no information on the validity of WPAI or its MCID in hepatitis C patients was found, the MCID for the WPAI has been reported to be ≥ 7 percentage points in patients suffering from Crohn disease.[45]

**Conclusion**

- A review using individual patient data from 15 phase 2 and 3 studies (N = 13,599 participants), in which the majority were patients with genotype 1 (N = 11,730), suggests that SVR12 is a reliable surrogate for SVR24. The authors suggest that SVR12 may become a new definition for SVR for regulatory approval.
- The generic EQ-5D HRQoL instrument has been widely used, but its psychometric properties have not been fully evaluated in CHC. Among patients with chronic hepatic diseases, the EQ-5D-5L version appears to be more feasible, consistent, and have a lower ceiling effect in comparison with the standard version. The MCID for the EQ-5D-5L among CHC patients remains unknown.
- SF-36, a generic health assessment questionnaire, has shown good construct validity in hepatitis C patients. A mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale has been reported. MCIDs for other dimensions or for the two component scores of the SF-36 for patients with CHC infection were not found in the literature, but the generally recommended MCID from the instrument developer for the PCS and MCS is 2 to 3 points.
- The CLDQ-HCV has shown good convergent and construct validities in hepatitis C patients. No information could be identified on the MCID of this instrument in hepatitis C, although one abstract cited an MCID of 0.5, perhaps in reference to the CLDQ-HCV.

- Although no information was found on the validity and MCID of FACIT-F in hepatitis C, the MCID in the FACIT-F ranged from 3 to 4 points in rheumatoid arthritis patients.
- Limited information was found on the validity of the WPAI questionnaire in hepatitis C; however, the MCID for the WPAI has been reported to be ≥ 7 percentage points in patients suffering from Crohn disease.

# REFERENCES


1. Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Can J Gastroenterol Hepatol [Internet]. 2014 May [cited 2016 Feb 1];28(5):243-50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049256
2. Hepatitis C in Canada: 2005-2010 surveillance report. Executive summary. Ottawa: Public Health Agency of Canada; 2012.
3. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008 Aug;48(2):418-31.
4. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007: final report [Internet]. Ottawa: Public Health Agency of Canada; 2009. [cited 2016 Feb 1]. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf
5. Centers for Disease Control and Prevention [Internet]. Atlanta (GA): Centers for Disease Control and Prevention. Surveillance for viral hepatitis - United States, 2011; 2013 Aug 19 [cited 2016 Feb 1]. Available from: http://www.cdc.gov/hepatitis/Statistics/2011Surveillance/Commentary.htm
6. Centre for Communicable Diseases and Infection Control, Infectious Disease Prevention and Control Branch. Hepatitis C in Canada: 2005-2010 surveillance report [Internet]. Ottawa: Public Health Agency of Canada; 2011. [cited 2016 Feb 1]. Available from: http://publications.gc.ca/collections/collection_2012/aspc-phac/HP40-70-2012-eng.pdf
7. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010 Feb;138(2):513-21.
8. Myers RP, Shah H, Burak KW, Cooper C, Feld JJ. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol [Internet]. 2015 Jan [cited 2016 Feb 1];29(1):19-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4334064
9. Canadian Agency for Drugs and Technologies in Health. Direct-acting antiviral agents for chronic hepatitis C genotype 1 [Internet]. Ottawa: CADTH; 2014. [cited 2016 Feb 1]. (CADTH therapeutic review, vol.2, issue 2B). Available from: http://www.cadth.ca/media/pdf/TR0007_HepC_ScienceReport_e.pdf
10. [Pr]Zepatier™ (elbasvir/grazoprevir): tablets, 50 mg/10 mg [product monograph]. Kirkland (QC): Merck Canada Inc.; 2016 Jan 19.
11. Zepatier™ (elbasvir and grazoprevir) tablets [product monograph] [Internet]. [Kenilworth (NJ)]: Merck & Co; 2016 Jan. [cited 2016 Feb 26]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208261Orig1s000lbl.pdf
12. Health Canada reviewer's report: Zepatier (elbasvir/grazoprevir) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2016 Jan.
13. Clinical study report: P068V01. A phase III randomized clinical trial to study the efficacy and safety of the combination regimen of GZR/EBR in subjects who have failed prior treatment with pegylated interferon and ribavirin (P/R) with chronic HCV GT1, GT4, and GT6 infection [**CONFIDENTIAL** internal manufacturer's report]. [Kenilworth (NJ)]: Merck Sharp & Dohme Corp.; 2015 May 6.

14. Clinical study report: P074V01. A phase II open-label clinical trial to study the efficacy and safety of the combination regimen of grazoprevir (GZR) and elbasvir (EBR), and sofosbuvir in treatment-naive subjects with chronic HCV GT1 and GT3 infection [**CONFIDENTIAL** internal manufacturer's report]. [Kenilworth (NJ)]: Merck Sharp & Dohme Corp.; 2015 Apr 2.
15. Clinical study report: P052V01. A phase II/III randomized clinical trial to study the efficacy and safety of the combination regimen of MK-5172 and MK-8742 in subjects with chronic hepatitis C virus infection and chronic kidney disease [**CONFIDENTIAL** internal manufacturer's report]. [Kenilworth (NJ)]: Merck Sharp & Dohme Corp.; 2015 Apr 24.
16. Clinical study report: P060V01. A phase III randomized clinical trial to study the efficacy and safety of the combination regimen of grazoprevir (GZR) and elbasvir (EBR) in treatment-naïve subjects with chronic HCV GT1, GT4, and GT6 infection [**CONFIDENTIAL** internal manufacturer's report]. [Kenilworth (NJ)]: Merck Sharp & Dohme Corp.; 2015 Apr 15.
17. Clinical study report: P061V01. A phase III open-label clinical trial to study the efficacy and safety of the combination regimen grazoprevir (GZR) and elbasvir (EBR) in treatment-naïve subjects with chronic HCV GT1, GT4, and GT6 infection who are co-infected with HIV [**CONFIDENTIAL** internal manufacturer's report]. [Kenilworth (NJ)]: Merck Sharp & Dohme Corp.; 2015 Apr 14.
18. Clinical study report: P035V01. A phase II randomized clinical trial to study the efficacy and safety of the combination regimen of MK-5172 and MK-8742 ± ribavirin (RBV) in subjects with chronic hepatitis C virus infection [**CONFIDENTIAL** internal manufacturer's report]. [Kenilworth (NJ)]: Merck Sharp & Dohme Corp.; 2015 Apr 28.
19. Clinical study report: p047. A phase II clinical trial to evaluate the efficacy and safety of a combination regimen of MK-5172 with/without MK-8742 and/or ribavirin (RBV) in treatment-naive subjects with chronic hepatitis C genotype 2, 4, 5 and 6 infection [**CONFIDENTIAL** internal manufacturer's report]. [Kenilworth (NJ)]: Merck Sharp & Dohme Corp.; 2015 Apr 13.
20. Clinical study report: P048v01. A phase II clinical trial to study the efficacy and safety of the combination regimen of MK-5172 + MK-8742 +ribavirin (R) in subjects with chronic hepatitis C virus infection who failed prior direct acting antiviral therapy [**CONFIDENTIAL** internal manufacturer's report]. [Kenilworth (NJ)]: Merck Sharp & Dohme Corp.; 2015 Mar 25.
21. Kamal SM. Acute hepatitis C: a systematic review. Am J Gastroenterol. 2008 May;103(5):1283-97.
22. Maheshwari A, Thuluvath PJ. Management of acute hepatitis C. Clin Liver Dis. 2010 Feb;14(1):169-76.
23. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet. 2008 Jul 26;372(9635):321-32.
24. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74.
25. Drugs for chronic hepatitis C infection: recommendations report [Internet]. Ottawa: CADTH; 2015 Nov. (CADTH therapeutic review; vol.3, no.1d). [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/pdf/TR0008_HepatitisC_RecsReport_e.pdf
26. [Pr]Victrelis® (boceprevir): 200 mg capsule [product monograph]. Kirkland (QC): Merck Canada Inc.; 2015 May 27.
27. [Pr]Daklinza™ (daclatasvir dihydrochloride): tablets, 30 and 60 mg [product monograph]. Montreal: Bristol-Myers Squibb Canada; 2015 Aug 12.
28. [Pr]Harvoni™ (ledipasvir/sofosbuvir): tablets, 90 mg/400 mg [product monograph]. Foster City (CA)/Mississauga (ON): Gilead Sciences Inc./Gilead Sciences Canada Inc.; 2015 Oct 20.

29. [Pr]Holkira™PAK: ombitasvir/paritaprevir/ritonavir, film coated tablets, 12.5/75/50 mg and dasabuvir (as dasabuvir sodium monohydrate), film-coated tablets, 250 mg [product monograph]. St-Laurent (QC): AbbVie Corporation; 2015 Oct 14.

30. [Pr]Galexos® (simeprevir sodium): 150 mg capsules [product monograph]. Toronto (ON): Janssen Inc.; 2015 Nov 15.

31. [Pr]Sovaldi® (sofosbuvir): tablets, 400 mg [product monograph]. Foster City (CA)/Mississauga (ON): Gilead Sciences Inc./Gilead Sciences Canada Inc.; 2015 Jul 21.

32. [Pr]Technivie™ (ombitasvir/paritaprevir/ritonavir): film-coated tablets 12.5/75/50 mg [product monograph]. St-Laurent (QC): AbbVie Corporation; 2015 Oct 20.

33. Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ari ZB, Zhao Y, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med. 2015 Jul 7;163(1):1-13.

34. Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV. 2015 Aug;2(8):e319-e327.

35. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour H Jr, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015 Oct 17;386(10003):1537-45.

36. CDR submission: grazoprevir/elbasvir tablets 100 mg/50 mg. Company: Merck Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Kirkland (QC): Merck Canada Inc.; 2015 Oct 27.

37. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015 Mar 21;385(9973):1075-86.

38. Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015 Mar 21;385(9973):1087-97.

39. Buti M, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, et al. Grazoprevir, elbasvir, and ribavirin for chronic hepatitis C virus genotype 1 infection after failure of pegylated interferon and ribavirin with an earlier-generation protease inhibitor: final 24-week results from C-SALVAGE. Clin Infect Dis. 2016 Jan 1;62(1):32-6.

40. Forns X, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. J Hepatol. 2015 Sep;63(3):564-72.

41. Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, et al. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2014 Aug;12(8):1349-59.

42. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes [Internet]. 2003 [cited 2016 Feb 22];1:79. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC317391

43. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005 May;32(5):811-9.

44. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire--general health version in patients with rheumatoid arthritis. Arthritis Res Ther [Internet]. 2010 [cited 2016 Feb 22];12(5):R177. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2991008

45. Louis E, Lofberg R, Reinisch W, Camez A, Yang M, Pollack PF, et al. Adalimumab improves patient-reported outcomes and reduces indirect costs in patients with moderate to severe Crohn's disease: results from the CARE trial. J Crohns Colitis. 2013 Feb;7(1):34-43.

46. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology [Internet]. 2005 Apr [cited 2016 Jan 25];41(4):790-800. Available from: http://onlinelibrary.wiley.com/doi/10.1002/hep.20659/epdf

47. Ware J, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. Determining importand differences in scores. In: User's manual for the SF-36v2 health survey. 2nd ed. Lincoln (RI): Quality Metric Inc.; 2007.

48. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2014 Aug 2;384(9941):403-13.

49. Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2014 Aug 2;384(9941):414-26.

50. Sulkowski MS, Naggie S, Lalezari J, Fessel WJ, Mounzer K, Shuhart M, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA. 2014 Jul 23;312(4):353-61.

51. Gordon CE, Balk EM, Becker BN, Crooks PA, Jaber BL, Johnson CA, et al. KDOQI US commentary on the KDIGO clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in CKD. Am J Kidney Dis. 2008 Nov;52(5):811-25.

52. Fabrizi F, Dixit V, Messa P, Martin P. Interferon monotherapy of chronic hepatitis C in dialysis patients: meta-analysis of clinical trials. J Viral Hepat. 2008 Feb;15(2):79-88.

53. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009 Aug 6;361(6):580-93.

54. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014 Feb;146(2):430-41.

55. Center for drug Evaluation and Research (CDER). Guidance for industry chronic hepatitis c virus infection: developing direct-acting antiviral drugs for treatment: draft guidance [Internet]. Silver Spring (MD): U.S. Department of Health & Human Services, U.S. Food and Drug Administration; 2013 Oct. [cited 2015 Dec 17]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf

56. Common Drug Review. Ledipasvir/sofosbuvir (Harvoni — Gilead Sciences Canada, Inc.) Indication: chronic hepatitis C virus genotype 1 infection in adults [Internet]. Ottawa: CADTH; 2015. (Clinical review report). [cited 2016 Feb 1]. Available from: https://www.cadth.ca/ledipasvir-sofosbuvir-4

57. Drugs for chronic hepatitis C infection: clinical review [Internet]. Ottawa: CADTH; 2016 Jan. (CADTH Therapeutic Review; Vol.3, No. 1b). [cited 2015 Nov 23]. Available from: https://www.cadth.ca/sites/default/files/pdf/TR0008_Clinical_Report-en.pdf

58. Lagging M, Brown A, Mantry PS, Ramji A, Weilert F, Vierling JM, et al. Grazoprevir plus peginterferon and ribavirin in treatment-naive patients with hepatitis C virus genotype 1 infection: a randomized trial. J Viral Hepat [Internet]. 2016 Feb [cited 2015 Dec 3];23(2):80-8. Available from: http://onlinelibrary.wiley.com/doi/10.1111/jvh.12464/epdf

59. Corrections to Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a nonrandomised, open-label trial. Lancet HIV 2015; 2: e319-27. The Lancet HIV. 2015;2(10):e416.

60. Roth D, Nelson DR, Bruchfeld A. Erratum: Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 45 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet, 2015; 386(10006):1537-45. The Lancet. 2015;386(10006):1824.

61. Corrections to Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV 2015; 2:319-327. The Lancet HIV. 2015;2(8):e316.

62. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013 Jun;144(7):1450-5.

63. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

64. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut [Internet]. 1999 Aug [cited 2016 Jan 26];45(2):295-300. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1727607

65. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993 Nov;4(5):353-65.

66. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology. 2010 Apr;51(4):1122-6.

67. Thorlund K, Druyts E, Mills EJ. SVR12 is higher than SVR24 in treatment-naive hepatitis C genotype 1 patients treated with peginterferon plus ribavirin. Clin Epidemiol [Internet]. 2014 [cited 2016 Jan 26];6:49-58. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897323

68. Yoshida EM, Sulkowski MS, Gane EJ, Herring RW Jr, Ratziu V, Ding X, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology. 2015 Jan;61(1):41-5.

69. Brooks R. EuroQol: the current state of play. Health Policy. 1996 Jul;37(1):53-72.

70. Sinnott PL, Joyce VR, Barnett PG. Guidebook: preference measurement in economic analysis [Internet]. Menlo Park (CA): Health Economics Research Center; 2007. [cited 2016 Jan 27]. Available from: http://www.herc.research.va.gov/files/BOOK_419.pdf

71. Scalone L, Ciampichini R, Fagiuoli S, Gardini I, Fusco F, Gaeta L, et al. Comparing the performance of the standard EQ-5D 3L with the new version EQ-5D 5L in patients with chronic hepatic diseases. Qual Life Res. 2013 Sep;22(7):1707-16.

72. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol. 2008 Feb;61(2):102-9.

73. Escheik C, Gerber L, Rover L, Arsalla Z, Otgonsuren M, Younossi Z. Validation of CLDQ-HCV as a health related quality of life (HRQL) instrument for patients with chronic hepatitis C (CH-C). Am J Gastroenterol. 2012;107:S159.

74. Loria A, Escheik C, Gerber L, Price JK, Younossi ZM. The chronic liver disease questionnaire-hepatitis C (CLDQ-HCV): a sensitive and valid health related quality of life instrument [abstract]. Hepatology. 2012;56 Suppl 1:646A.

75. Moon J, Kallman J, Younossi Z, Winter PM, Fang Y, Gerber L. T1001: validation of chronic liver disease-HCV version (Cldq-HCV) with fatigue severity scale (Fss) [abstract]. Gastroenterology [Internet]. 2010 [cited 2016 Jan 27];138(5 Suppl 1):S833. Available from: http://www.gastrojournal.org/article/S0016-5085%2810%2963840-1/pdf

76. Price JK, Moon J, Winter PM, Fang Y. SU1337: hemoglobin level is associated with the physical functioning, activity, energy, and vitality aspects of health-related quality of life in patients with chronic hepatitis C (Ch-C) [abstract]. Gastroenterology [Internet]. 2011 [cited 2016 Jan 27];140(5 Suppl 1):S461. Available from: http://www.gastrojournal.org/article/S0016-5085(11)61896-9/pdf

77. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.

78. Blackburn S, McCool R, Panter C, Young V, Peterson S, Mitchell L. IN1: interviews with patients with chronic hepatitis C (CHC) virus infection document unmet needs, content validity, and comprehension of pros for clinical trials [abstract]. Value Health [Internet]. 2013 [cited 2016 Jan 27];16(3):A6. Available from: http://www.valueinhealthjournal.com/article/S1098-3015%2813%2900105-8/pdf