International Journal of Women's Health

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ORIGINAL RESEARCH

# Elbasvir/grazoprevir in women with hepatitis C virus infection taking oral contraceptives or hormone replacement therapy

This article was published in the following Dove Press journal:
*International Journal of Women's Health*

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**Introduction:** Some direct-acting antiviral regimens for hepatitis C virus (HCV) infection pose safety or efficacy concerns if coadministered with drugs containing ethinyl estradiol. The present analysis was conducted to examine the impact of concomitant oral contraceptive pills (OCP) or hormone replacement therapy (HRT) during treatment with elbasvir (EBR)/grazoprevir (GZR) in women with HCV genotype (GT)1 or GT4 infection.

**Methods:** This is a post hoc, integrated retrospective analysis of female participants with HCV GT1 or GT4 infection who received EBR 50 mg/GZR 100 mg once daily for 12 weeks in phase 2/3 clinical trials. The primary end point was sustained virologic response at 12 weeks after therapy completion (SVR12). For this analysis, participants were stratified according to whether they received OCP or HRT during the original treatment study.

**Results:** A total of 1,022 women with HCV GT1 or GT4 infection were included (receiving OCP/HRT, n=81; not receiving OCP/HRT, n=941). Most participants receiving OCP/HRT were treatment-naive (79%), noncirrhotic (91.4%), and aged >35 years (71.6%). SVR12 rates were similar in women receiving OCP/HRT and those not receiving OCP/HRT (95.1% vs 96.3%). SVR12 rates remained high across all subgroups within the population receiving OCP/HRT: SVR12 rates were 94.6%, 100%, and 100% in participants with GT1a, GT1b, and GT4 infection, and all women aged 18–35 years achieved SVR (21/21). Treatment-related adverse events occurred in 40.7% (33/81) and 30.1% (283/941) of women receiving and those not receiving OCP/HRT, respectively.

**Conclusion:** The efficacy and safety of EBR/GZR administered for 12 weeks was similar in women receiving OCP/HRT and those not on OCP/HRT. These data indicate that EBR/GZR can be safely used for the treatment of HCV GT1 or GT4 infection in women receiving concomitant OCP/HRT.

**Keywords:** clinical trial, ethinyl estradiol, levonorgestrel, NS5A inhibitor, NS3/4A protease inhibitor

In recent years, there has been a dramatic increase in the number of newly reported cases of hepatitis C virus (HCV) infection worldwide, driven largely by the increase in injection drug use in younger adults.[1,2] As a result of this increase in HCV infection among younger adults, the prevalence of HCV infection has also increased notably among women of child-bearing potential. The number of women of reproductive age with HCV infection in the United States National Notifiable Diseases Surveillance System increased from 15,550 in 2006 to 31,039 in 2014.[3] Furthermore, estimates also suggest that between 2011 and 2014, the national rate of HCV detection among women of childbearing age in the United States increased

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http://doi.org/10.2147/IJWH.S203022

by 22% (from 139 to 169 per 100,000 women) and the proportion of infants born to women with HCV infection increased by 68% (from 1 in 536 [0.19%] births to 1 in 308 births).[4] Successful treatment of HCV infection in this emerging population therefore needs to be mindful of the specific characteristics of this particular population, one of which is the use of ethinyl estradiol–containing medications as oral contraceptive therapy. Oral contraceptive pills (OCPs) have the potential for drug–drug interactions, particularly when coadministered with inhibitors or inducers of cytochrome 450 (CYP 3A) or uridine 5′-diphosphoglucuronosyltransferases.[5–9] Some direct-acting antiviral regimens for HCV infection pose safety or efficacy concerns if coadministered with OCPs or hormone replacement therapies (HRT) that contain ethinyl estradiol.[10–12]

The fixed-dose combination of elbasvir (EBR) 50 mg/grazoprevir (GZR) 100 mg is approved in the United States, Europe, and other countries worldwide for the treatment of people with HCV genotype (GT) 1 or GT4 infection.[13,14] The individual drugs have been shown to be potent in vitro,[15–18] and in clinical trials, this combination was highly effective across a wide range of people with HCV infection and various comorbidities.[19–24] The clinical pharmacology of EBR/GZR is also well-established, enabling EBR/GZR to be used in a range of individuals with HCV infection who are receiving concomitant medications.[13,14] Phase 1 clinical trials have shown no clinically meaningful impact of multiple doses of EBR/GZR on the pharmacokinetics of ethinyl estradiol/levonorgestrel in healthy female adults without HCV infection, suggesting that EBR/GZR can be coadministered to women with HCV infection who are taking OCPs to prevent pregnancy.[25] Ethinyl estradiol and levonorgestrel have the potential for drug–drug interactions when coadministered with inhibitors or inducers of CYP3A or uridine 5′-diphospho-glucuronosyltransferases. EBR is a substrate of CYP3A/P-glycoprotein (P-gp) and an inhibitor of breast cancer resistance protein, and GZR is a substrate of CYP3A/P-gp and organic anion transporter polypeptide 1B1/1B3 and is also a weak CYP3A inhibitor and a breast cancer resistance protein inhibitor. Based on these metabolic pathways, neither ethinyl estradiol nor levonorgestrel is expected to alter either EBR or GZR pharmacokinetics.[25] In order to fully characterize the clinical safety and efficacy profile of EBR/GZR in women with HCV infection who are taking OCPs or HRT, a post hoc, retrospective analysis was conducted to examine the impact of concomitant OCP or HRT in women with HCV GT1 or GT4 infection receiving EBR/GZR in phase 2/3 clinical trials.

# Methods

This was an integrated retrospective analysis of data from 12 international phase 2/3 clinical trials. The original studies were carried out in accordance with the Declaration of Helsinki, current guidelines on Good Clinical Practices, and local ethical and legal requirements (Table 1). All participants in these studies provided voluntary written informed consent before trial entry. Previous reports have described the methodology and primary outcomes from these studies (C-SCAPE[26] [NCT01932762; Protocol PN047-03]; C-SURFER[21] [NCT02092350/Protocol PN052]; C-EDGE CO-INFECTION[22] [NCT02105662/Protocol PN061]; C-EDGE Treatment-Naive[19] [NCT02105467/Protocol PN060]; C-EDGE Treatment-Experienced[20] [NCT02105701/Protocol PN068]; C-WORTHY[27,28] [NCT01717326/Protocol PN035]; C-EDGE CO-STAR[24] [NCT02105688/Protocol PN062]; C-EDGE Head-2-Head[29] [NCT02358044/Protocol PN077]; Japan phase 2/3 study[30] [NCT02203149/Protocol PN058]; C-EDGE-IBLD[23] [NCT02252016/Protocol PN065]; C-CORAL[31] [NCT02251990/Protocol PN067]; C-SALT[32] [NCT02115321/Protocol PN059].

## Participants

Female participants with HCV GT1 or GT4 infection from these 12 studies were included in the present analysis (Table 1). All original studies had generally similar inclusion and exclusion criteria. In brief, participants were aged >18 years with chronic HCV infection and HCV RNA >10,000 IU/mL at baseline. Participants were treatment-naive or had previously failed interferon-based HCV therapy, were HCV monoinfected or HCV/HIV coinfected, and were either noncirrhotic or had compensated Child-Pugh A cirrhosis. In these studies, cirrhosis was defined as liver biopsy consistent with METAVIR fibrosis score of F4; FibroScan® >12.5 kPa within 12 months of study entry; or aspartate aminotransferase (AST)-to-platelet ratio >2.0 and FibroTest >0.75 within 12 months of study entry. Other comorbidities present in this population were chronic kidney disease stage 4 or 5 (including those on hemodialysis),[21] inherited blood disorders,[23] and those receiving opioid agonist therapy.[24] Individuals with decompensated liver disease (as indicated by a presence or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs of advanced liver disease), or evidence of hepatocellular carcinoma were excluded from the original studies.

**Table 1** Original treatment studies

| Study name (ClinicalTrials.gov identifier/ protocol number) | Participant population/HCV genotype | Women not receiving OCP/HRT (n=941) | Women receiving OCP/HRT (n=81) |
|---|---|---|---|
| C-WORTHY (NCT01717326/PN035)[27,28] | Cirrhotic and noncirrhotic; TN/TE/ GT1 | 44 (4.7) | 5 (6.2) |
| C-SCAPE (NCT01932762/PN047-03)[26] | Non-GT1 | 3 (0.3) | 1 (1.2) |
| C-SURFER (NCT02092350/PN052)[21] | CKD; TN; cirrhotic and noncirrhotic/GT1 | 54 (5.7) | 4 (4.9) |
| Japan phase 2/3 study (NCT02203149/PN058)[30] | Japanese; cirrhotic and noncirrhotic; TN/TE/GT1 | 218 (23.2) | 9 (11.1) |
| C-EDGE Treatment-Naive (NCT02105467/PN060)[19] | TN/GT1 or GT4 | 164 (17.4) | 21 (25.9) |
| C-EDGE CO-INFECTION (NCT02105662/ PN061)[22] | HCV/HIV/coinfected; TN/GT1 or GT4 | 33 (3.5) | 2 (2.5) |
| C-EDGE CO-STAR (NCT02105688/PN062)[24] | TN on opioid agonist therapy/GT1 or GT4 | 57 (6.1) | 11 (13.6) |
| C-EDGE IBLD (NCT02252016/PN065)[23] | TN/TE/GT1 or GT4 | 31 (3.3) | 6 (7.4) |
| C-CORAL (NCT02251990/PN067)[31] | Asia-Pacific; TN/GT1 or GT4 | 228 (24.2) | 13 (16.0) |
| C-EDGE Treatment-Experienced (NCT02105701/ PN068)[20] | TE/GT1 or GT4 | 34 (3.6) | 5 (6.2) |
| C-EDGE Head-2-Head (NCT02358044/PN077)[29] | TN/TE/GT1 or GT4 | 71 (7.5) | 3 (3.7) |
| C-SALT (NCT02115321/PN059)[32] | Noncirrhotic, TN/TE/GT1 | 4 (0.4) | 1 (1.2) |

**Abbreviations:** CKD, chronic kidney disease; GT, genotype; HCV, hepatitis C virus; HRT, hormone replacement therapy; IBLD, inherited blood disorders; OCP, oral contraceptive pills; TE, treatment-experienced; TN, treatment-naive.

## Treatment

To be included in this analysis, participants were required to have received EBR 50 mg/GZR 100 mg once daily, administered either as a coformulated fixed-dose combination tablet or as separate entities, for 12 weeks. In the United States and Europe, EBR/GZR plus ribavirin for 16 weeks is approved for the treatment of certain HCV-infected patient subgroups; however, the 12-week regimen of EBR/GZR (no ribavirin) represents the most commonly utilized regimen in current clinical practice. The present analysis will therefore focus solely on individuals who received the 12-week regimen in the phase 2/3 clinical trials.

## Outcomes

The primary end point of all original studies was sustained virologic response at 12 weeks after completion of therapy (SVR12). Plasma HCV RNA levels were measured using the Cobas® AmpliPrep/Cobas® TaqMan® HCV test (version 2.0, Roche Molecular Diagnostics, Branchburg, NJ, USA) with a lower limit of quantitation of 25 IU/mL in the phase 2 studies and 15 IU/mL in the phase 3 studies. In all studies, relapse was defined as detectable HCV RNA following the end of therapy after undetectable HCV RNA at the end of therapy.

## Analyses

This was a retrospective analysis of data from phase 2/3 clinical trials. For the purposes of this analysis, female participants were stratified according to whether they were receiving OCP (yes, no) or HRT (yes, no) for ≥7 days during treatment with EBR/GZR in the original treatment study. Efficacy and safety comparisons were made between participants who were and those who were not receiving OCP/HRT. Efficacy analyses included all eligible participants who received ≥1 dose of study (the full analysis set). A supportive analysis is also described that was based on the modified full analysis set population, which excluded participants who discontinued from the trial for reasons unrelated to the study drug. Safety analyses included all participants who received ≥1 dose of study medication.

## Results

A total of 1,022 women with HCV GT1 or GT4 infection who received EBR/GZR for 12 weeks were included in the full analysis set, including 81 participants receiving OCP/HRT (75 [92.6%] of whom were on OCP/HRT for the complete 12 weeks of treatment), and 941 women not receiving OCP/HRT. Concomitant therapies used by the 81 women receiving OCP/HRT are listed in Table S1.There were a total of 100 reports of OCP/HRT use among the 81 women who received OCP/HRT (who included those who may have stopped and restarted therapy and therefore had >1 record of OCP/HRT use). The most common reasons for use of OCP/HRT medications were contraception (n=45), hormone replacement therapy (n=21), vaginitis/vaginal atrophy/vaginal dryness (n=7), and uterine bleeding (n=5). (Table S2). Most of the women receiving OCP/HRT were originally treated in the C-EDGE Treatment-Naive[19] (n=21, 25.9%), C-CORAL[31] (n=13, 16%), CO-STAR[24] (n=11, 13.6%), and the Japanese phase 2/3 studies[30] (n=9, 11%) (Table 1). Most participants receiving OCP/HRT had HCV GT1a (n=38, 46.9%) or GT1b (n=39, 48.1%) infection, were treatment-naive (n=64, 79%), noncirrhotic (n=74, 91.4%), and were aged >35 years (n=58, 71.6%). Women not receiving OCP/HRT were more likely to have HCV GT1b infection than those receiving OCP/HRT (70.0% vs 48.1%, respectively) and aged >35 years (89.7% vs 71.6%, respectively) (Table 2). Participants receiving opioid agonist therapy enrolled from the CO-STAR study[24] represented 13.6% (11/81) of women receiving OCP/HRT and 6.1% (57/941) of women not receiving OCP/HRT.

**Table 2** Participant demographics

| Characteristic, n (%) | Women not receiving OCP/HRT (n=941) | Women receiving OCP/HRT (n=81) |
|---|---|---|
| Age, years | | |
| 18–35 years | 97 (10.3) | 23 (28.4) |
| >35 years | 844 (89.7) | 58 (71.6) |
| HCV genotype, n (%) | | |
| GT1a | 245 (26.0) | 38 (46.9) |
| GT1b | 659 (70.0) | 39 (48.1) |
| GT1-other | 6 (0.6) | 0 |
| GT4 | 31 (3.3) | 4 (4.9) |
| Baseline viral load | | |
| ≤800,000 IU/mL | 299 (31.8) | 35 (43.2) |
| >800,000 IU/mL | 642 (68.2) | 46 (56.8) |
| HCV/HIV coinfection | | |
| HCV monoinfected | 897 (95.3) | 79 (97.5) |
| HCV/HIV coinfected | 44 (4.7) | 2 (2.5) |
| Treatment history | | |
| Treatment-experienced | 156 (16.6) | 17 (21.0) |
| Treatment-naive | 785 (83.4) | 64 (79.0) |
| Cirrhosis | | |
| Yes | 151 (16.0) | 7 (8.6) |
| No | 777 (82.6) | 74 (91.4) |
| Unknown | 13 (1.4) | 0 (0) |
| *IL28B* genotype | | |
| CC | 409 (43.5) | 24 (29.6) |
| Non-CC | 525 (55.8) | 56 (69.1) |
| Unknown | 7 (0.7) | 1 (1.2) |

**Abbreviations:** HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRT, hormone replacement therapy; OCP, oral contraceptive pills.

## Virologic response

In the full analysis set, sustained virologic response (SVR) rates were similar in women receiving OCP/HRT and those not receiving OCP/HRT (95.1% [77/81] vs 96.3% [906/941]) (Table 3). A total of 4 women receiving OCP/HRT (relapse, n=2; nonvirologic failure, n=2) and 35 women not receiving OCP/HRT (relapse, n=21; reinfection, n=2; nonvirologic failure, n=12) failed to achieve SVR12. When participants with nonvirologic failure who discontinued treatment for reasons unrelated to study medication were excluded from the modified full analysis set, SVR12 rates were 97.5% (77/79) and 97.5% (906/929) in women receiving and those not receiving OCP/HRT, respectively.

Subgroup analysis indicates that SVR12 rates remained high across all subgroups within the population of women receiving OCP/HRT (Figure 1). Rates of SVR12 were high in participants with HCV GT1a, GT1b, and GT4 infection (94.6%, 100%, and 100%, respectively) and in both treatment-naive, and treatment-experienced participants (98.4% and 93.7%, respectively). All women aged 18–35 years achieved SVR (100%, 21/21) compared with 96.6% of those aged >35 years (56/58). Among the 8 participants with cirrhosis receiving OCP/HRT in this analysis, 7 achieved SVR (85.7%) and 1 relapsed. SVR rates also remained >90% regardless of baseline viral load, HIV coinfection status, or *IL28B* genotype.

Two participants receiving OCP/HRT experienced virologic failure. A 46-year-old woman with β-thalassemia

**Table 3** Virologic outcomes

| | Women not receiving OCP/HRT (n=941) | Women receiving OCP/HRT (n=81) |
|---|---|---|
| SVR12, n/N (%) | | |
| Full analysis set* | 906/941 (96.3%) | 77/81 (95.1%) |
| Modified full analysis set† | 906/929 (97.5%) | 77/79 (97.5%) |
| Non-SVR12, n (%) | | |
| Relapse | 21 (2.2%) | 2 (2.4%) |
| Reinfection | 2 (0.2%) | 0 (0%) |
| Nonvirologic failure | 12 (1.2%) | 2 (2.4%) |

**Notes:** *Full analysis set: includes all participants who received ≥1 dose of study medication. †Modified full analysis set: excludes nonvirologic failures.
**Abbreviations:** HRT, hormone replacement therapy; OCP, oral contraceptive pills; SVR12, sustained virologic response at 12 weeks after completion of therapy.

and HCV GT1a infection with cirrhosis who was receiving estradiol/norethindrone relapsed at follow-up week 12 after having undetectable HCV RNA at the end of treatment. She had no baseline nonstructural protein 5A (NS5A) resistance-associated substitutions (RASs) and had treatment-emergent Q30H and Y93H RASs at the time of failure. She was a previous null responder to peginterferon/ribavirin, had an elevated baseline international normalized ratio of 2.7 (normal range, 0.9–1.1), and had a baseline HCV RNA of 4,203,381 IU/mL. She was randomized to deferred treatment, and per protocol received EBR/GZR for 12 weeks after an initial placebo treatment period. She reported no interruption to study medication. Her concomitant medications included deferasirox, fluticasone, fentanyl, levothyroxine, and ciprofloxacin. A 59-year-old treatment-naive, noncirrhotic woman with HCV GT1a infection receiving estradiol experienced relapse at follow-up week 8 after achieving undetectable HCV RNA at follow-up week 4. Her baseline HCV RNA was 1,939,436 IU/mL, and she had no baseline NS5A RASs. She had received EBR/GZR for 12 weeks and

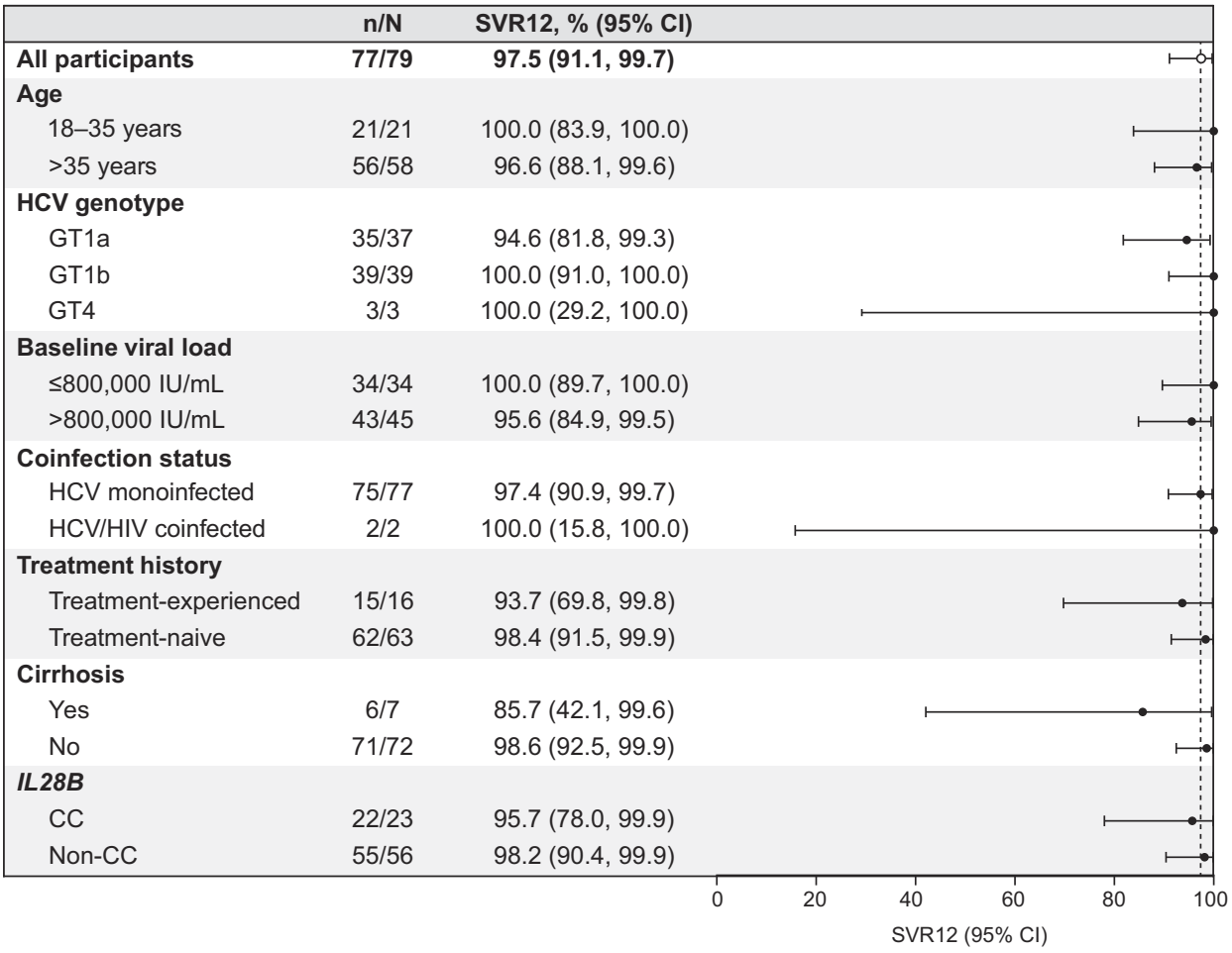


**Figure 1** SVR12 subgroup analysis among women on OCP/HRT receiving EBR/GZR for 12 weeks.
**Abbreviations:** CI, confidence interval; EBR, elbasvir; GZR, grazoprevir; HIV, human immunodeficiency virus; HRT, hormone replacement therapy; OCP, oral contraceptive pills; SVR12, sustained virologic response at 12 weeks after completion of therapy.

reported no interruption to study medication. At virologic failure, she had a Y93 RAS. Her concomitant medications included: enalapril, atenolol, pentoxifylline, ketorolac, omeprazole, fluticasone, insulin, etodolac, and albuterol.

## Adverse events

Adverse events (AEs) were reported by 80.2% (65/81) of women receiving OCP/HRT and by 65.7% (618/941) of those not receiving OCP/HRT (Table 4). Similarly, treatment-related AEs were reported by 40.7% (33/81) and 30.1% (283/941) of women receiving and those not receiving OCP/HRT, respectively, while the respective rates of serious AEs were 2.8% (26/941) and 6.2% (5/81) (Table S3). Five serious AEs in 3 participants were considered related to treatment with EBR/GZR: elevated alanine aminotransferase (ALT) and AST (n=1 each; same participant), gastritis erosive and hypophosphatemia (n=1 each; same participant), and atrial fibrillation (n=1). None of the participants was receiving concomitant OCP/HRT. Five serious AEs were reported by 5 participants who were receiving concomitant OCP/HRT (n=1 each): hemorrhagic erosive gastritis, muscular weakness, bipolar disorder, schizophrenia, and uterine hemorrhage; none were considered related to study drug.

On-treatment changes in liver transaminase levels, bilirubin, and hemoglobin were generally similar in women not receiving and those receiving OCP/HRT. During the phase 2/3 trials of EBR/GZR, elevations of ALT and/or AST levels were observed late in the course of therapy (ie, after treatment week 4) among a proportion of participants.[33] In the current analysis, ALT/AST elevations >500 IU/L or ALT/AST elevations >100 IU/L and >3× baseline were reported in 18 (1.9%) women not receiving OCP/HRT and 2 (2.4%) women receiving OCP/HRT. Of those participants receiving OCP/HRT, the first ALT elevation was reported by a 56-year-old noncirrhotic white woman with HCV GT4

**Table 4** Adverse events

| | Women not receiving OCP/HRT (n=941) | Women receiving OCP/HRT (n=81) |
|---|---|---|
| Any AE, n (%) | 618 (65.7) | 65 (80.2) |
| Drug-related AE, n (%) | 283 (30.1) | 33 (40.7) |
| Serious AE, n (%) | 26 (2.8) | 5 (6.2) |
| Drug-related SAEs, n (%) | 3 (0.3) | 0 (0) |
| Discontinuation due to an AE, n (%) | 7 (0.7) | 1 (1.2) |
| Death, n (%) | 2 (0.2) | 0 (0) |
| ALT, n/N (%) | | |
| 1.1–2.5× baseline | 33/940 (3.5) | 5/81 (6.2) |
| >2.5–5.0× baseline | 7/940 (0.7) | 0/81 (0) |
| >5.0× baseline | 14/940 (1.5) | 2/81 (2.5) |
| AST, n/N (%) | | |
| 1.1–2.5× baseline | 33/940 (3.5) | 8/81 (9.9) |
| >2.5–5.0× baseline | 12/940 (1.3) | 1/81 (1.2) |
| >5.0× baseline | 8/940 (0.9) | 2/81 (2.5) |
| Bilirubin, n/N (%) | | |
| >2.5–5.0× baseline | 8/940 (0.9) | 0/81 (0) |
| >5.0–10.0× baseline | 0/940 (0) | 0/81 (0) |
| >10.0× baseline | 0/940 (0) | 0/81 (0) |
| Hemoglobin, n/N (%) | | |
| 8.5 to <10.0 | 50/940 (5.3) | 4/81 (4.9) |
| <8.5 | 14/940 (1.5) | 0/81 (0) |
| ALT/AST elevation, n/N (%)* | 18/941 (1.9) | 2/81 (2.4) |

**Notes:** *First instance of ALT or AST >500 IU/L not associated with virologic failure OR first instance of ALT or AST >3× baseline AND >100 IU/L not associated with virologic failure.

**Abbreviations:** AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HRT, hormone replacement therapy; OCP, oral contraceptive pills.

infection receiving promestriene. At baseline her ALT was 62 IU/L and her clinical course remained uneventful until treatment week 8, when her ALT levels increased to >500 IU/L. She had no abdominal symptoms, fever, or rash, and her direct bilirubin (0.16 mg/dL), total bilirubin (0.39 mg/dL), and international normalized ratio (INR) (1.1) were normal. Treatment with EBR/GZR was discontinued per protocol (ALT or AST >500 IU/L). Her ALT event was confounded by the ingestion of alcohol the day before the abnormal ALT test and the self-administration of several doses of etifoxine for anxiety, a drug with known hepatotoxic potential. She underwent extensive evaluation, all of which did not reveal an infectious or obstructive etiology. The participant discontinued medication on day 59, and the elevation resolved within 4 weeks. She achieved SVR12. Other concomitant medications taken during treatment were desloratadine, acyclovir, aspirin, ibuprofen, and pinaverium. The second ALT elevation was reported by a 33-year old noncirrhotic white woman with HCV GT1b infection and β-thalassemia receiving estradiol valerate (+) norgestrel. Her baseline ALT was 54 IU/L, but at treatment week 8 she had a transient elevation of ALT to 331 IU/L that resolved by the next laboratory evaluation at treatment week 2 (ALT=34 IU/L). Both her total bilirubin and INR values were consistent with day 1 values. Her ALT elevation resolved by day 73 with continued treatment. The participant achieved SVR12. Other concomitant medications taken during treatment were deferoxamine, esomeprazole, amoxicillin, and levothyroxine.

## Discussion

Data from this retrospective, post hoc analysis indicate that the safety and efficacy profile of EBR/GZR administered for 12 weeks is generally unaffected by concomitant OCP/HRT. SVR12 rates were >95% regardless of OCP/HRT administration. Excluding participants who did not have a virologic outcome, SVR12 was achieved by 97.5% of those receiving and those not receiving OCP/HRT. The safety profile of EBR/GZR in women receiving OCP/HRT was also generally similar to that in women not receiving OCP/HRT. Drug-related serious AEs were reported only by women not receiving OCP/HRT.

Young adults represent a rapidly growing segment of the population with new HCV infection, driven largely by the increasing parenteral use of recreational drugs. Treatments for HCV infection therefore require continual re-evaluation to ensure that they meet the requirements of this changing epidemiology. While younger people do not have the same comorbidities and hence do not have the same requirements for medication that are seen in older individuals, evaluation of drug–drug interactions remains an important consideration in establishing the clinical profile of HCV therapies. Ethinyl estradiol–containing products, used as OCPs and also as HRT, are a common therapy across a broad range of women with HCV infection.

The potential of EBR or GZR to impact the pharmacokinetics of an oral contraceptive in healthy, postmenopausal or oophorectomized women was recently examined in 2 drug–drug interaction studies.[25] In these one-way studies, EBR did not substantially alter the plasma exposure of ethinyl estradiol or levonorgestrel. Coadministration of GZR also did not substantially alter the plasma exposure of ethinyl estradiol; however, the plasma area under the curve from zero to infinity ($AUC_{0-\infty}$) of levonorgestrel was increased by 23% in the presence of GZR.[25] These data indicate that EBR does not substantially alter the plasma exposure of ethinyl estradiol/levonorgestrel. The small increase in levonorgestrel $AUC_{0-\infty}$ seen in the presence of GZR is consistent with GZR being a weak CYP3A inhibitor and is not considered clinically significant.[13,14]

Careful consideration of OCP/HRT use in women who are taking direct-acting antiviral agents is warranted. In contrast to the phase 1b study by Marshall et al, a 2- to 3-fold increase in norelgestromin and norgestrel concentrations is reported when ethinyl estradiol/norgestimate is coadministered with ombitasvir/paritaprevir/ritonavir/dasabuvir tablets.[10] In addition, during clinical trials with the ombitasvir/paritaprevir/ritonavir/dasabuvir combination regimen, ALT elevations were significantly more frequent in women who were using ethinyl estradiol–containing medications such as OCPs, contraceptive patches, or contraceptive vaginal rings compared with those not receiving these ethinyl estradiol–containing products.[10] Based on these findings, ethinyl estradiol–containing medications are contraindicated in women receiving the ombitasvir/paritaprevir/ritonavir/dasabuvir combination therapy.[10] Similarly, coadministration of ethinyl estradiol in individuals with HCV infection receiving glecaprevir/pibrentasvir has also been reported to increase the risk of ALT elevations and is not recommended.[11] Elevated serum concentrations of GZR have also been associated with increased serum transaminase elevations. However, in the present analysis, on-treatment changes in liver transaminase levels, bilirubin, and hemoglobin were generally similar in the participants receiving OCP/HRT and those not receiving OCP/HRT,

consistent with no elevation in serum concentrations of GZR in the presence of OCP/HRT therapies.

Limitations of this analysis include the post hoc, retrospective nature of the study. The populations of women receiving and those not receiving OCP/HRT were not randomized in this analysis, and thus differences in these populations exist, such as the proportions of patients with GT1b infection (48.1% vs 70.7%) and of those aged 18–35 years (28.4% vs 9.5%). Analysis of specific participant subgroups, such as those with HIV coinfection, cirrhosis, or HCV GT4 infection, are also limited by the relatively small number of women receiving OCP/HRT in these subgroups. The analysis is also limited owing to the heterogeneous nature of OCP and HRT medications. For the purposes of this analysis, all OCP/HRT medications were grouped into a single population to increase the population sample size under investigation; however, it should be noted that because of the heterogeneous nature of the medications, care should be exercised when drawing conclusions based on any individual OCP or HRT medication. Our data also cannot exclude the possibility of minor drug-drug interactions between EBR/GZR and components of OCP/HRT therapy other than ethinyl estradiol/levonorgestrel.

In conclusion, the efficacy and safety of EBR/GZR administered for 12 weeks was similar in female participants receiving concomitant OCP/HRT compared with those not on concomitant OCP/HRT. Rates of SVR12 were high regardless of treatment history, presence of cirrhosis, baseline viral load, or age. Similarly, rates of AEs and drug-related AEs were generally similar in women receiving OCP/HRT and those not receiving OCP/HRT. These data support observations from a phase 1 drug-interaction study[25] indicating that EBR/GZR can be safely used for the treatment of HCV GT1 or GT4 infection in women receiving concomitant OCP/HRT.

## Data sharing statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

## Acknowledgment

We extend our gratitude to the participants, their families, investigators, and site personnel who participated in this study. Medical writing and editorial assistance was provided by Tim Ibbotson, PhD, of ApotheCom, Yardley, PA, and funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD). The trials included in this integrated analysis were sponsored and funded in full by MSD. MSD contributed to the trial design, study execution and management, data collection, and statistical analyses of the original treatment studies, and also conducted the integrated analysis described in this report. Portions of the data described in the manuscript were previously presented at The International Liver Congress; April 11–15, 2018; Paris, France [abstract #801].

## Disclosure

Dr Hézode has received personal fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and MSD. Dr Kwo received grants from the Regenstrief Institute and Target Registeries, has received grants and personal fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, MSD, and Janssen, and has received personal fees from Quest, Arrowhead, Surrozen, Ferring, Conatus, Dova and Shinogi. Dr Sperl has received grants from Gilead Sciences and personal fees from Gilead Sciences, MSD, AbbVie, Herbacos Recordati, and Intercept. Drs Hwang, Robertson, and Haber are current employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and stockholders in Merck & Co., Inc., Kenilworth, NJ, USA. Drs Long and Talwani were employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, at the time that the study was conducted. The authors report no other conflicts of interest in this work.

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# Supplementary materials

**Table S1** OCP and HRT therapies coadministered with EBR/GZR in contributing phase 2/3 studies

| OCP/HRT Concomitant Therapies,* n (%) | N=81 |
|---|---|
| Estradiol | 17 (21.0) |
| Ethinyl estradiol (+) levonorgestrel | 11 (13.6) |
| Medroxyprogesterone acetate | 6 (7.4) |
| Desogestrel (+) ethinyl estradiol | 5 (6.2) |
| Raloxifene hydrochloride | 5 (6.2) |
| Desogestrel | 4 (4.9) |
| Cyproterone acetate (+) ethinyl estradiol | 3 (3.7) |
| Drospirenone (+) ethinyl estradiol | 3 (3.7) |
| Dydrogesterone | 3 (3.7) |
| Estradiol (+) norethindrone acetate | 3 (3.7) |
| Estrogens, conjugated | 3 (3.7) |
| Levonorgestrel | 3 (3.7) |
| Estriol | 2 (2.5) |
| Estrogens, conjugated (+) medroxyprogesterone acetate | 2 (2.5) |
| Ethinyl estradiol (+) norelgestromin | 2 (2.5) |
| Ethinyl estradiol (+) norgestimate | 2 (2.5) |
| Norethindrone | 2 (2.5) |
| Progesterone | 2 (2.5) |
| Bazedoxifene | 1 (1.2) |
| Dienogest | 1 (1.2) |
| Dienogest (+) estradiol valerate | 1 (1.2) |
| Drospirenone (+) estradiol | 1 (1.2) |
| Drospirenone (+) ethinyl estradiol betadex clathrate | 1 (1.2) |
| Estradiol valerate (+) norgestrel | 1 (1.2) |
| Ethinyl estradiol | 1 (1.2) |
| Ethinyl estradiol (+) gestodene | 1 (1.2) |
| Ethinyl estradiol (+) norethindrone acetate | 1 (1.2) |
| Ethinyl estradiol (+) norgestrel | 1 (1.2) |
| Prasterone (+) progesterone (+) testosterone | 1 (1.2) |
| Promestriene | 1 (1.2) |

**Notes:** *Concomitant therapies included were taken for ≥7 days during treatment with EBR/GZR.
**Abbreviations:** HRT, hormone replacement therapy; OCP, oral contraceptive pills.

**Table S2** Reasons for using OCP/HRT medications

| n (%) | N=100* |
|---|---|
| Contraception | 45 (45) |
| Hormone replacement | 21 (21) |
| Vaginitis/atrophy/dryness | 7 (7) |
| Uterine bleeding | 5 (5) |
| Low progesterone | 2 (2) |
| Osteoporosis prophylaxis | 2 (2) |
| Premature ovarian failure | 2 (2) |
| Hypogonadism | 2 (2) |
| Other | 8 (8) |
| No reason provided | 6 (6) |

**Notes:** *81 patients reported a total of 100 instances of OCP/HRT use (including patients who may have stopped/started therapy and therefore have >1 record for OCP/HRT use).
**Abbreviations:** HRT, hormone replacement therapy; OCP, oral contraceptive pills.

**Table S3** Serious adverse events

| Serious AE | Women not receiving OCP/HRT (n=941) | Women receiving OCP/HRT (n=81) |
|---|---|---|
| Any | 26 | 5 |
| Atrial fibrillation | 3 | 0 |
| Pneumonia | 2 | 0 |
| Alanine aminotransferase increased | 1 | 0 |
| Aspartate aminotransferase increased | 1 | 0 |
| Bipolar disorder | 0 | 1 |
| Cardiac arrest | 1 | 0 |
| Cardiac failure | 1 | 0 |
| Cardiac sarcoidosis | 1 | 0 |
| Cataract | 1 | 0 |
| Colitis ischemic | 1 | 0 |
| Completed suicide | 1 | 0 |
| Drug abuse | 1 | 0 |
| Extremity necrosis | 1 | 0 |
| Fluid overload | 1 | 0 |
| Gastritis erosive | 1 | 0 |
| Gastrointestinal hemorrhage | 1 | 0 |
| Hemorrhagic erosive gastritis | 0 | 1 |
| Hepatic encephalopathy | 1 | 0 |
| Hypertensive crisis | 1 | 0 |
| Hypophosphatemia | 1 | 0 |
| Iron deficiency anemia | 1 | 0 |
| Laceration | 1 | 0 |
| Muscular weakness | 0 | 1 |
| Seizure | 1 | 0 |
| Overdose | 1 | 0 |
| Pulmonary edema | 1 | 0 |
| Pleural effusion | 1 | 0 |
| Schizophrenia | 0 | 1 |
| Sciatica | 1 | 0 |
| Sickle cell anemia with crisis | 1 | 0 |
| Skin ulcer | 1 | 0 |
| Sudden hearing loss | 1 | 0 |
| Tooth abscess | 1 | 0 |
| Uterine hemorrhage | 0 | 1 |

**Abbreviations:** AE, adverse event; HRT, hormone replacement therapy; OCP, oral contraceptive pills.