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ORIGINAL ARTICLE

Sustainable and equivalent improvements in symptoms and functional well-being following viral cure from ledipasvir/sofosbuvir versus elbasvir/grazoprevir for chronic hepatitis C infection: Findings from the randomized PRIORITIZE trial

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Abstract

The PRIORITIZE trial (clinicaltrials.gov: NCT02786537) was the first comparative effectiveness study to directly compare ledipasvir/sofosbuvir (LDV/SOF) and elbasvir/grazoprevir (EBR/GZR) for the treatment of chronic hepatitis C virus (HCV). A secondary aim of this study was to compare LDV/SOF and EBR/GZR on sustainable changes in several HCV-associated symptoms and functional well-being in patients who achieved sustained virological response (SVR). PRIORITIZE, a randomized controlled trial conducted between 2016 and 2020, evaluated change in six PROMIS® symptom scores (fatigue, sleep disturbance, cognitive disturbance, nausea, diarrhoea, abdominal pain) and functional well-being using the disease-specific HCV-PRO instrument. Survey assessments were administered at baseline, early post-treatment (median = 6 months) and late post-treatment (median = 21 months). Constrained longitudinal linear mixed-effects models were used to evaluate within-treatment change and between-treatment differences. Data from 793 participants (average 55 years old, 57% male, 44% black, 17% with cirrhosis) were analysed. From baseline to early post-treatment, 5 out of 6 symptoms and functional well-being significantly improved (all p's $< .05$). In the LDV/SOF arm, mean changes ranged from −3.73 for nausea to −6.41 for fatigue and in the EBR/GZR, mean changes ranged from −2.19 for cognitive impairment to −4.67 for fatigue. Change of >3 points was consider clinically meaningful. Improvements in most symptoms slightly favoured LDV/SOF, although the magnitude of differences between the regimens were small. Both regimens demonstrated significant improvements in symptoms and functional well-being that were sustained during the late post-treatment phase. EBR/GZR and LDV/SOF regimens had clinically equivalent and durable improvements in HCV symptoms and functional well-being up to two years after SVR.

KEYWORDS
comparative effectiveness, direct acting antiviral, instrument, patient-reported outcomes, survey, sustained virological response

1 | INTRODUCTION

Individuals living with chronic hepatitis C virus (HCV) infection often complain of debilitating or bothersome symptoms such as fatigue, depression, anxiety, cognitive dysfunction, sleep disturbance, aches and pains and gastrointestinal symptoms that are associated with poor health-related quality of life (HRQOL).[1-4] HCV can cause inflammatory and immune abnormalities early during the infection even prior to cirrhosis and can lead to extrahepatic manifestations that may be partially responsible for chronic symptoms.[5-10]

All-oral, direct acting antiviral (DAA) regimens can eradicate HCV in approximately 95% of patients treated.[11] Phase III registration trials of DAA medications did not use active comparator groups but rather compared regimens to historical controls or within DAA trials, to regimens with and without ribavirin (RBV).[12,13] Achieving viral cure has been associated with improvements in symptoms and HRQOL in registration trials and in uncontrolled observational studies.[14-16] Despite widespread global use of several different DAA regimens, comparative effectiveness studies that directly compare different DAAs on patient-centred outcomes have not been conducted until recently. Results from the PRIORITIZE study, the only randomized controlled trial to compare efficacy and tolerability of different DAA regimens, recently demonstrated equivalence between DAA regimens on treatment efficacy, safety, and drug side effect profiles.[17] Beyond sustained virological response (SVR) rates, other characteristics of treatment matter to patients and stakeholders, such as the magnitude and durability of improvements in HCV symptoms and functioning.[18] Whether differences exist between DAA regimens in terms of amelioration of HCV-associated symptoms or improvements in functioning following SVR, both in the short term and the long term, has not been determined, but would provide valuable data for patients, clinicians and other stakeholders.

The objective of this longitudinal study was to provide a direct comparison of improvements in HCV symptoms and functional well-being up to two years after SVR, in patients with genotype 1 HCV who were treated with ledipasvir/sofosbuvir (LDV/SOF) or elbasvir/grazoprevir (EBR/GZR) in the PRIORITIZE trial.[17]

2 | MATERIALS AND METHODS

2.1 | Study overview and design

A detailed description of the PRIORITZE study is reported elsewhere.[17] Briefly, PRIORITIZE was a multi-site randomized, pragmatic clinical trial. Phase II of the PRIORITIZE trial was designed to compare LDV/SOF (Harvoni®, Gilead Sciences Inc) and EBR/GZR (Zepatier™ Merck and Co) in patients infected with HCV genotype 1 on several primary and secondary outcomes. PRIORITIZE was conducted within the HCV-TARGET Network infrastructure and included 34 US sites.[19] In Phase II, 1455 patients were randomized (stratified by cirrhosis status and genotype 1 subtype) equally to LDV/SOF or EBR/GZR. Recruitment began in June 2016 and final data collection ended on 31 August 2020. All participating sites received Institutional Review Board approval and all patients provided written consent before enrolment.

2.2 | Treatment regimens

Participants treated with LDV/SOF took one tablet (90/400 mg) daily for 8 or 12 weeks and RBV could be added, based on local provider's discretion. Participants treated with EBR/GZR took one tablet (50/100 mg) daily for 12 weeks. Participants infected with NS5A-resistant genotype 1a (any location) received 16 weeks of EBR/GZR plus twice-daily RBV dosed according to body weight (five or six RBV pills per day). Study drug was supplied to participants randomized to EBR/GZR (donated by Merck) while LDV/SOF medications relied on patients' insurance. Participants' HCV treatment was managed according to local site standard of care, which generally followed US prescribing information and HCV guidelines.[11] After treatment, patients were followed for an additional 12 weeks to determine SVR12. Patients were to be followed for the study for up to three years after treatment or according to local standard of care practices.

2.3 | Study participants

Patients 18 years of age or older with HCV infection (genotype 1a or 1b) were invited to participate by local hepatology providers if one of the two DAA regimens were deemed clinically appropriate. Exclusion criteria included the following: current or historical evidence of hepatic decompensation unless decompensation was prior to successful liver transplant, Child-Turcotte-Pugh (CTP) stage B or C cirrhosis, pregnancy or breastfeeding status, or health insurance that did not cover LDV/SOF. When a preliminary benefits investigation identified a non-LDV/SOF regimen as the preferred regimen, the patient was counted as a screen failure and was not randomized. Participants with HIV, organ transplant, and other medical, psychiatric or substance use disorders were eligible. For this report, the study cohort was restricted to enrolled participants who were treated with LDV/SOF or EBR/GZR, achieved SVR status, and completed at least one patient-reported outcome (PRO) survey at baseline or during post-treatment follow-up.

2.4 | Clinical and PRO data collection

As with the HCV-TARGET registry, clinical and laboratory data were sourced from patients' electronic medical records.[19] Safety and efficacy laboratory markers during DAA treatment and long-term follow-up were based on local provider discretion. All medical record data related to standard clinical care visits and procedures were redacted by local site research coordinators and submitted to a centrally located team for abstraction and data entry into a secure, web-based Research Electronic Data Capture System (REDCap).

Once patients were assigned to a treatment regimen, PRO symptom surveys were administered up to five times during the study at the following three assessment points: (1) pre-treatment (baseline: [60 days before to 7 days after start date]); (2) early post-treatment (~6 months post EOT: [EOT to 450 days after EOT]); and (3) late post-treatment (~20 months post EOT: >450 days after EOT).

Participants were given the option of completing the surveys using a unique REDCap survey link sent to their pre-approved email address or by conducting phone surveys with a centralized call centre at the University of Florida and having responses entered directly into REDCap. Survey completion took around 25 minutes and participants were reimbursed $25 each time they completed the assessments.

2.5 | Primary outcomes

The PRO measures were selected after consultation with the HCV Patient Engagement Group (HCV-PEG) that served as our patient partners during study design.[20]

HCV symptoms were evaluated using six instruments from the National Institutes of Health's Patient-Reported Outcomes Measurement Information System® (PROMIS®).[21,22] All PROMIS scores are scaled to standardized T-scores, with a mean of 50 and standard deviation of 10. For most of the adult PROMIS domain measures, the mean 50 and standard deviation of 10 is centred on the U.S. general population. The exceptions are that the PROMIS Sleep Disturbance measure was centred on a clinical sample and the general population and the PROMIS gastrointestinal (GI) domains (abdominal pain, diarrhoea, nausea/vomiting) are centred on the general population who reported at least one GI symptom.[24] The psychometric properties of these PROMIS instruments have been evaluated in patients with HCV undergoing DAA therapy and found to be satisfactory.[25] Lower scores indicate less symptom burden on all six instruments. Studies in other medical populations suggest that the minimally important difference between groups ranges from 2 to 5 points.[26-29] In a previous observational study of HCV patients who completed PROMIS measures, a 5% change was recommended by the HCV-PEG and established as the minimally meaningful important change threshold and this equated to approximately a 3-point change in a symptom score.[15]

2.5.1 | Fatigue

The PROMIS Fatigue 7a short form includes questions such as 'In the past a bath?' The 7 items have a 5-point response scale from 'Never' to 'Always'. T-scores could range from 29.4 to 83.2.

2.5.2 | Sleep disturbance

The PROMIS Sleep Disturbance 8a short form includes items such as 'In the past 7 days, I was satisfied with my sleep', '…had difficulty falling asleep' and '…my sleep was restless'. The 8 items have a 5-point response scale from 'Not at all' to 'Very much'. T-scores could range from 29.4 to 83.2, with lower scores indicating less fatigue. T-scores could range from 30.5 to 77.5.

2.5.3 | Cognitive impairment

The PROMIS Applied Cognition -General Concerns 8a short form was used to measure patients' perceptions of cognitive functioning. Items include items such as 'In the past 7 days, I have had trouble forming my thoughts', '…my thinking has been slow', and '…I have had trouble concentrating'. The 8 items have a 5-point response scale from 'Never' to 'Very often'. T-scores could range from 23.3 to 62.7.

2.5.4 | Abdominal pain

The PROMIS Gastrointestinal Belly Pain 5-item short form was used to measure belly pain. The first question is 'In the past 7 days, how often did you have belly pain?' If the participant response is 'Never', they are instructed to skip to the last question, only completing two questions. If any belly pain is endorsed, participants respond to all 5 questions. A 5-point response scale was used that ranged from 'Never' to 'More than once a day', 'Not bad at all' to 'Very bad', or 'Not at all' to 'Very much' depending on the question. T-scores could range from 33.9 to 80.0.

2.5.5 | Nausea/vomiting

The PROMIS Gastrointestinal Nausea/Vomiting 4-item short form was used to measure nausea and vomiting. The first question is 'In the past 7 days, how often did you have nausea – a feeling like you could vomit' and '…how often did you have poor appetite?' If the participant response is 'Never', they are instructed to skip one question and only complete three questions. If nausea is endorsed, participants respond to all 4 questions. The items have a 5-point response scale from 'Never' to 'Always'. T-scores could range from 40.6 to 80.1.

2.5.6 | Diarrhoea

The PROMIS Diarrhoea 6a short form includes, 'In the last 7 days, how many days did you have loose or watery stools?' and 'How often did you feel like you needed to empty your bowels right away or else you would have an accident?' Skip patterns are used if participants do not report any symptoms, such that 2, 4 or 6 items are answered. Items have a 5-point response scale from 'Not at all' to 'Very much', 'Never' to 'More than once a day' or 'No Days' to '6–7 Days' depending on the question. T-scores could range from 39.9 to 75.2.

2.5.7 | Functional well-being

The HCV-PRO disease-specific instrument was used to measure functional well-being and HRQOL.[30,31] The measure was developed according to guidelines set forth by the U.S. Food and Drug Administration and has shown satisfactory reliability and validity.[30,31] The instrument includes 16 items that measure physical and emotional functioning, productivity, intimacy and quality of life related to HCV. Responses range from 1 = 'All of the time' to 5 = 'None of the time'. The sum of the 16 items is transformed to a scale from 0 to 100, with *lower* HCV-PRO scores indicating lower *functional well-being*. A 5% change was recommended by the HCV-PEG as the minimally important threshold which equates to approximately a 4-point change in the HCV-PRO score.[15]

2.5.8 | Sociodemographic and clinical covariates

Data sourced from patients' electronic medical records for this analysis included age (<65/≥65 years), sex (Female/Male), race (Black/White/other), genotype (1a/1b), health insurance (Medicaid/Medicare/private/uninsured/Other), cirrhosis status (yes/no), prior HCV treatment status (yes/no), RBV use (yes/no), psychiatric comorbidities (yes/no), use of proton pump inhibitor (PPI) medication (yes/no), and total number of medical comorbidities (0, 1, 2+). Health insurance status was classified as follows: (i) Medicaid if they had any combination of insurance with Medicaid present (e.g. Medicaid+Medicare), (ii) Medicare if included Medicare only or combined with supplemental or private insurance and (iii) private if having private insurance with no Medicaid or Medicare.

2.6 | Statistical analysis

To obtain point estimates and 95% confidence interval (CI) estimates of population mean responses and mean differences, the main analysis for each PRO measure relied on a constrained longitudinal linear mixed-effects model.[32-34] This approach treats the baseline PRO score as one of the outcomes, along with the early post-treatment score and the late post-treatment score. This type of modelling is advantageous for several reasons: (1) patients can be included even if they have missing values, (2) we can take advantage of the correlations (shared information) among the patients' longitudinal measures for purposes of coping with missing values, (3) we avoid problems inherent to modelling change scores with/without conditioning on baseline as a covariate, (4) improved accuracy of variance–covariance assumptions can be achieved, (5) estimation of time-specific mean levels and mean changes is straightforward and (6) the approach facilitates evaluation of time-specific covariate effects. Importantly, due to randomization and to improve precision and accuracy, we assumed that there were no DAA treatment effects at baseline; this important constraint improves precision and accuracy. The model was constrained by the assumption that the treatment regimens cannot have an effect at baseline (pre-treatment). The models accounted for DAA regimen as-randomized and the following covariates: cirrhosis status (Yes/No), treatment experience status (Yes/No), genotype 1 subtype (1a/1b), sex (Male/Female), age-group (<65/65+) and race (Black/White/Other), along with terms representing the interaction of regimen with cirrhosis, genotype and race.

Sensitivity analyses were conducted to evaluate the robustness or fragility of the main results by modifying the statistical methods and assumptions used. Specifically, we evaluated the impact of the following: (i) removing the baseline constraint from the model; (ii) using 'as-treated' classification instead of 'as-randomized' (difference of $n = 6$); (iii) using inverse probability weighting to cope with drop-out after randomization, (iv) using inverse probability weighting as if the data were from an observational study; and (v) including additional covariates or fewer covariates in the model. The additional covariates of interest were RBV use (Yes/No), health insurance type (Uninsured/Medicare/Medicaid/Private/Other), psychiatric comorbidities (Yes/No), use of PPI (Yes/No) and total number of medical comorbidities (0–2/3–4/5+). The sensitivity analyses also included analysis of residuals and assessment of variance inflation due to multi-collinearity among the covariates. Sensitivity analyses were only used to guide our level of trust in the main results.

In interpreting estimates of mean changes and mean differences, we considered a change of >3 points on the PROMIS symptom scores and a change of >4 points on the HCV-PRO score to be clinically meaningful.[15]

The statistical computations were performed using SAS System software version 9.4 (SAS Institute). PROMIS T-scores were computed using R software, version 3.6.1, and RStudio software, version 1.3.1093 (RStudio Inc.).

3 | RESULTS

3.1 | Study flowchart

Of 1455 patients who were randomized into the PRIORITIZE trial, 700 were randomized to EBR/GZR and started treatment, of whom 556/586 (95%) had documented SVR and 498 had completed at least one PRO survey. Of 428 participants randomized to LDV/SOF and started treatment, 349/359 (97%) had documented SVR and 295 had completed at least one PRO survey. A total of 793 participants were included in this analysis (Figure 1).

3.2 | Participant characteristics at baseline

The two cohorts were similar on most baseline characteristics (Table 1). Psychiatric comorbidity at baseline was slightly more prevalent in patients randomized to EBR/GZR (38%) than in patients randomized to LDV/SOF (32%). Medicaid insurance was more prevalent

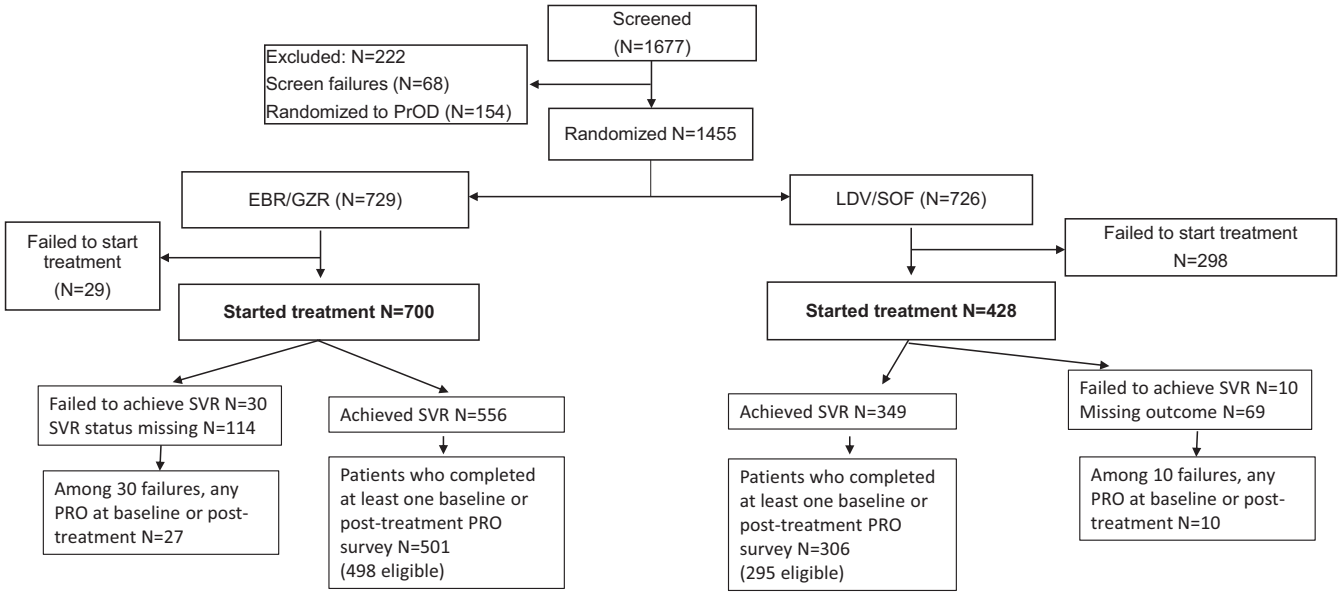


FIGURE 1 Study flowchart

in the EBR/GZR arm (46%) than in the LDV/SOF arm (26%), while private/commercial insurance was more prevalent in LDV/SOF arm (42%) than in the EBR/GZR arm (32%).

3.3 | Treatment-specific mean change from baseline to early post-treatment

Five of the six PRO measures showed clinically meaningful improvement from baseline to early post-treatment for both regimens (Table 2 and Figures 2–4). Sleep disturbance was the only symptom that did not exhibit a clinically meaningful mean change from baseline. In the LDV/SOF arm, the estimates of mean change ranged from −3.73 for nausea/vomiting to −6.41 for fatigue. In the EBR/GZR, the estimates of mean change ranged from −2.19 for cognitive impairment to −4.67 for fatigue.

Functional well-being showed clinically meaningful improvement from baseline to early post-treatment in the EBR/GZR arm (5.09 [1.55, 8.62]) and was twice that magnitude in the LDV/SOF arm (10.80 [6.10, 15.51]).

3.4 | Treatment-specific mean change from baseline to late post-treatment

For both treatment regimens, clinically meaningful symptom improvements from baseline to early post-treatment were sustained during the late post-treatment phase (Table 2 and Figures 2–4). For instance, in the LDV/SOF arm, mean changes from baseline to early and late post-treatment were respectively, −6.41 and −6.66 points for fatigue; and −3.73 and −4.48 for nausea. In the EBR/GZR arm, mean changes from baseline to early and late post-treatment were respectively, −4.67 and.

−4.57 for fatigue and −2.30 and −2.66 for nausea. Functional well-being continued to improve from early to late post-treatment in both treatment arms, with mean changes from baseline of 10.80 and 12.28 in the LDV/SOF arm, and 5.09 and 9.25 in the EBR/GZR arm, during early and late post-treatment, respectively.

3.5 | Between-treatments differences in mean change from baseline

For mean change in the symptom scores at early and late post-treatment, the magnitudes of the differences were not statistically or clinically significant between the two treatment regimens, with one exception for change in belly pain at early post-treatment that favoured LDV/SOF by 3.04 points ([0.08, 6.00], $p = .04$). (Table 3 and Figures 2–4). The remaining estimates of differences between the two regimens ranged from 0.57 to 1.82 during early post-treatment and −0.07 to 2.09 during late post-treatment phase. For functional well-being, the LDV/SOF arm experienced greater improvement early post-treatment (−5.72 [−10.58, −0.86], $p = .02$) but those differences attenuated during the late post-treatment phase (−3.03 [−8.77, 2.71, $p = .30$]).

3.6 | Sensitivity analyses

The sensitivity analyses conducted produced estimates that closely approximated the main results, thus supporting trust in the main results and suggesting that selection biases were negligible. For instance, sensitivity analyses that unconstrained the baseline scores and included additional covariates in the models (RBV use, health insurance type, psychiatric disorder, use of PPI and total number of medical comorbidities) did not alter the main results (Figure S1).

TABLE 1 Patient characteristics

	EBR/GZR, *n* (%) *N* = 498	LDV/SOF, *n* (%) *N* = 295	Overall, *n* (%) *N* = 793
Age			
Mean (SD)	54.2 (12.0)	57.4 (10.3)	55.4 (11.5)
Sex			
Male	274 (55)	179 (61)	453 (57)
Female	224 (45)	116 (39)	340 (43)
Race			
Black	227 (46)	131 (44)	358 (45)
White	233 (47)	151 (51)	384 (48)
Other	38 (8)	13 (4)	51 (6)
Ethnicity			
Not Hispanic	457 (92)	267 (91)	724 (91)
Hispanic	33 (7)	18 (6)	51 (6)
Not reported	8 (2)	10 (3)	18 (2)
Insurance			
Medicaid	231 (46)	76 (26)	307 (39)
Medicare	81 (16)	67 (23)	148 (19)
Private	161 (32)	124 (42)	285 (36)
Uninsured	22 (4)	25 (8)	47 (6)
Other	3 (1)	3 (1)	6 (1)
Genotype			
1A	379 (76)	214 (73)	593 (75)
1B	119 (24)	81 (27)	200 (25)
Treatment experience			
No	447 (90)	258 (87)	705 (89)
Yes	51 (10)	37 (13)	88 (11)
Cirrhosis			
No	416 (84)	241 (82)	657 (83)
Yes	82 (16)	54 (18)	136 (17)
RBV use			
No	459 (92)	284 (96)	743 (94)
Yes	39 (8)	11 (4)	50 (6)
Psychiatric comorbidities			
No	307 (62)	202 (68)	509 (64)
Yes	191 (38)	93 (32)	284 (36)

Abbreviations: EBR/GZR, elbasvir/grazoprevir; LDV/SOF, ledipasvir/sofosbuvir; RBV, Ribavirin.

4 | DISCUSSION

Patients chronically infected with HCV, as well as other stakeholders, need information about the short-term and long-term harms and benefits of available DAA treatments in order to make educated decisions about their treatment options.[18,35] Although the likelihood of viral cure is paramount, knowledge of other harms and benefits (e.g. impact on functioning, HRQOL, pre-existing symptoms and comorbidities, extrahepatic manifestations) are also important to consider.[18,36] DAA registration trials were the first to demonstrate substantial improvements in HRQOL shortly following treatment.[37,38] Observational studies have also demonstrated improvements in HRQOL and patient-reported symptoms during DAA therapy and in the months following viral cure.[15,16,39,40] However, these studies were not designed to conduct head-to-head comparisons of different DAA medications in order to determine whether one treatment is superior to another on patient-centred outcomes.

The PRIORITIZE study was the first comparative effectiveness trial to directly compare two DAA medications for the treatment of chronic HCV.[17] In the current report, we compared patients randomized to LDV/SOF and EBR/GZR on change in six symptoms associated with HCV and functional well-being up to three years after patients achieved viral cure. The main finding was that *both* EBR/GZR and LDV/SOF regimens conferred substantial improvements in symptoms and functional well-being in the months following viral cure, but more importantly, these improvements remained durable two years after treatment ended (median = 21 months). Though patients on LDV/SOF appeared to experience greater improvements, on average, the mean differences between the two treatment regimens were negligible and usually not clinically meaningful. Various sensitivity analyses supported the main results; that is, the addition of other covariates to the models, such as RBV use, health insurance status, or psychiatric illness, did not alter the main results.

Our findings are consistent with prior studies citing benefits to HRQOL and symptoms but expand upon the existing literature by conducting a head-to-head comparison of two different DAA regimens. Negligible differences in patient outcomes were found between patients randomized to EBR/GZR and LDV/SOF and this study demonstrated long-term durability of symptom and functional improvements up to two years after treatment. [4,14,15,16,39,40,41] After viral cure, five of the six symptom scores showed clinically meaningful improvements in both DAA arms; mean levels of sleep disturbance also showed improvements in both arms, but the magnitudes of improvement were small and not clinically meaningful. This finding is somewhat inconsistent with other studies that have demonstrated improvement in sleep after viral cure, though two of these studies used different sleep instruments. [39,42,43] Finally, this study is one of the few to evaluate long-term improvements in under-studied gastrointestinal symptoms such as abdominal pain, nausea and diarrhoea and to demonstrate clinically meaningful improvements for these distressing symptoms.

The results from this study have both clinical and health policy implications. When SVR rates are clinically equivalent among DAA regimens[17], other aspects of treatment regimens may become salient to stakeholders, especially patients.[18] Had we discovered superiority of one DAA regimen over the other in safety or patient-reported outcomes, these data may have swayed stakeholders to favour one regimen. Our data suggest that patients and clinicians can anticipate similar long-term improvements in symptoms and functioning in patients with characteristics similar to those who participated in

TABLE 2 Within-treatment changes in patient-reported symptoms and functional well-being from baseline to post-treatment phases

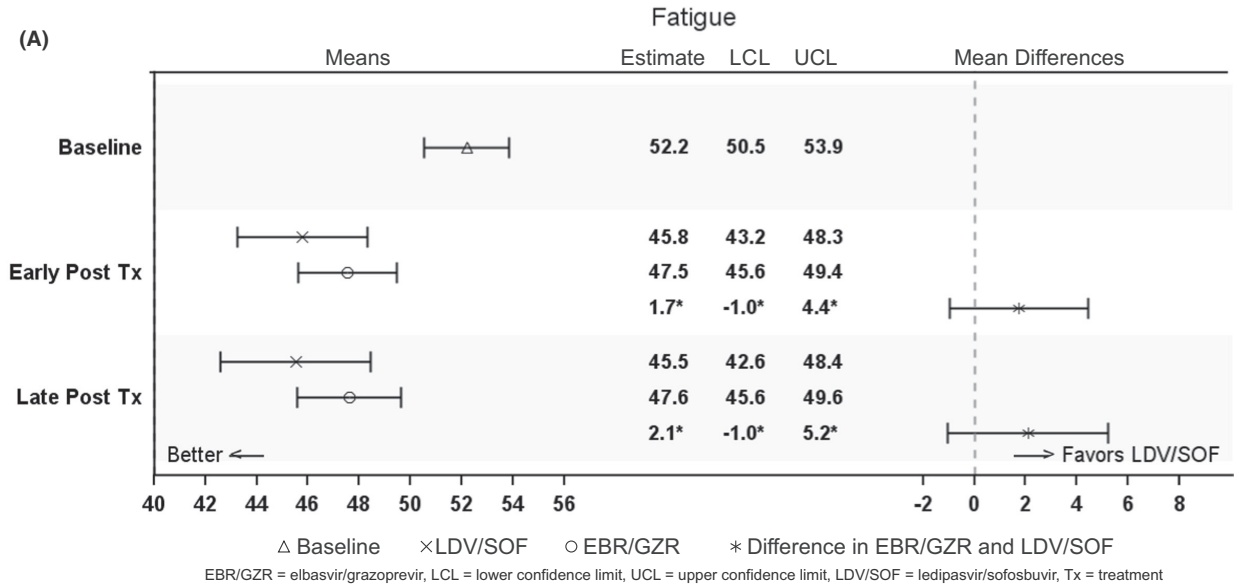
		Early post-treatment				Late post-treatment			
Concept	**Regimen**	**Estimatet**	**Lower**	**Upper**	**Pr > |t|**	**Estimatet**	**Lower**	**Upper**	**Pr > |t|**
Nausea/vomiting	EBR/GZR	−2.30	−4.01	−0.59	.0083	−2.66	−4.48	−0.85	.0040
	LDV/SOF	−3.73	−5.99	−1.47	.0012	−4.48	−7.05	−1.91	.0006
Belly pain	EBR/GZR	−3.11	−5.30	−0.93	.0053	−2.78	−5.06	−0.49	.0174
	LDV/SOF	−6.15	−9.08	−3.22	<.0001	−4.53	−7.75	−1.32	.0058
Diarrhoea	EBR/GZR	−3.72	−5.29	−2.14	<.0001	−3.07	−4.71	−1.43	.0003
	LDV/SOF	−5.36	−7.45	−3.26	<.0001	−3.74	−6.02	−1.45	.0014
Fatigue	EBR/GZR	−4.67	−6.70	−2.64	<.0001	−4.57	−6.72	−2.42	<.0001
	LDV/SOF	−6.41	−9.08	−3.74	<.0001	−6.66	−9.70	−3.62	<.0001
Sleep disturbance	EBR/GZR	−0.30	−1.47	0.87	.6186	−1.07	−2.31	0.17	.0907
	LDV/SOF	−0.87	−2.47	0.74	.2890	−1.37	−3.14	0.39	.1270
Cognitive impairment	EBR/GZR	−2.19	−3.66	−0.73	.0034	−2.47	−4.03	−0.91	.0019
	LDV/SOF	−4.02	−6.05	−1.99	.0001	−2.40	−4.63	−0.18	.0344
HCV-PRO	EBR/GZR	5.09	1.55	8.62	.0049	9.25	5.45	13.05	<.0001
	LDV/SOF	10.80	6.10	15.51	<.0001	12.28	6.80	17.76	<.0001

Note: [t]Point estimates and 95% confidence intervals of mean differences within each regimen. Symptoms were assessed by the PROMIS instruments. Negative numbers suggest reduction in symptoms. Positive numbers for HCV-PRO suggest improved functioning.

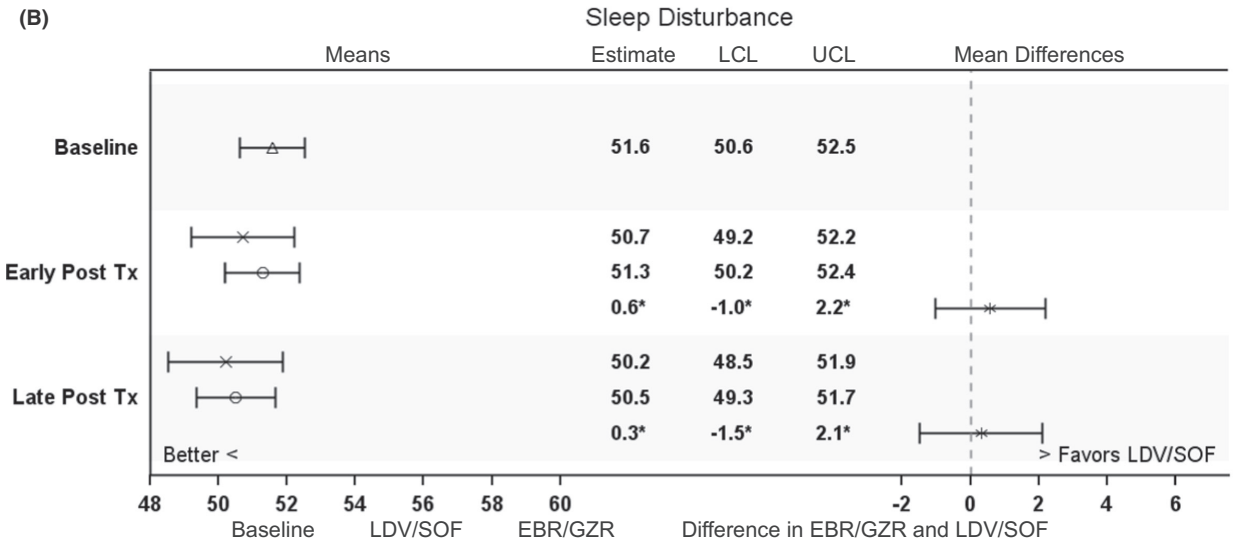
PRIORITIZE and should feel reassured in selecting either treatment that is available to them. Collectively, the empirical evidence suggests profound health benefits are realized by patients who are able to access DAA therapy and achieve viral cure. Qualitative and quantitative studies with patients before and after DAA therapy suggest that improvements in physical symptoms such as fatigue and abdominal pain may lead to subsequent improvements in social and work-related functioning. Similarly, reductions in anxiety and fear may lead to subsequent improvements in psychological, emotional, social and work-related functioning.[36,43,44] These downstream holistic benefits of being cured of HCV should be communicated during patient-provider treatment discussions, especially among individuals who may be treatment reticent[40] and should convince health policy makers and insurance payers of the widespread and far-reaching positive value of DAA treatment on all infected individuals and society at large.

Several limitations of this study are noteworthy. First, patients were not required to complete baseline PRO surveys in order to be eligible to participate; therefore, there were missing data at baseline. Relatedly, due to the pragmatic trial design and no mandatory research visits during follow-up, many patients were lost to follow-up. Nonetheless, we coped with issues of missing data with well-established statistical methods and our sensitivity analyses (using methods such as inverse probability weighting) produced estimates of treatment effects that closely approximated those obtained in our main results. Second, the scope of this study did not include measurement of all factors that could potentially influence both the outcomes and the occurrence of missing values. For example, we cannot be certain that confounding bias was not caused by unmeasured variables such as alcohol and substance use before or after treatment. In general, our sensitivity analyses included use of methods (e.g. inverse probability weighting) aimed at addressing selection biases. Also, we note that prior studies have demonstrated that alcohol and drug use in particular may have minimal influence on clinical outcomes following DAA therapy;[44-47] in fact, some studies suggest that patients using drugs or other vulnerable populations may actually reap even greater health benefits from viral cure.[15,40] Third, we observed an imbalance of some patient characteristics at baseline due to drop-out and exclusion of patients who did not achieve SVR; however, our sensitivity analyses indicated that these baseline differences did not appear to bias our estimates of treatment effects. Fourth, with rapid advances in the landscape of HCV treatment, newer pangenotypic DAA treatment regimens (glecaprevir/pibrentasvir, velpatasvir/sofosbuvir) have been approved and are predominantly prescribed frequently in the US, but we were unable to collect comparative data on these newer regimens due to the timing of the study. Finally, the findings from this study do not automatically generalize to the general population of people living with HCV in the US, including those with decompensated cirrhosis, people who inject drugs, Veterans and people who are incarcerated.

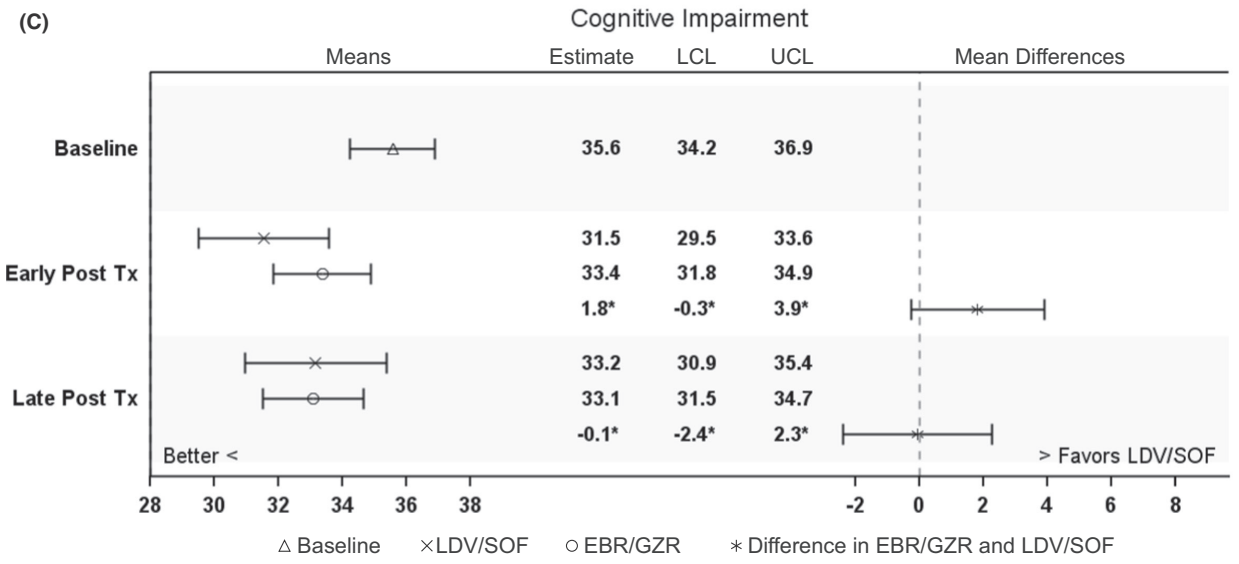
To conclude, in this novel comparative effectiveness study of two DAA regimens to examine patient functioning and symptom resolution after HCV viral cure, we found steadfast long-term amelioration of fatigue, cognitive impairment, gastrointestinal symptoms and functioning up to two years after viral cure. Importantly, no clinically meaningful differences were observed between the EBR/GZR and LDV/SOF treatment arms. Comparative effectiveness studies such as PRIORITIZE are essential to compare newer medical therapies for all chronic liver diseases. In the absence of unbiased, head-to-head comparisons of drug therapies, key stakeholders are unable to adequately weigh the trade-offs and risks and benefits of



EBR/GZR = elbasvir/grazoprevir, LCL = lower confidence limit, UCL = upper confidence limit, LDV/SOF = ledipasvir/sofosbuvir, Tx = treatment

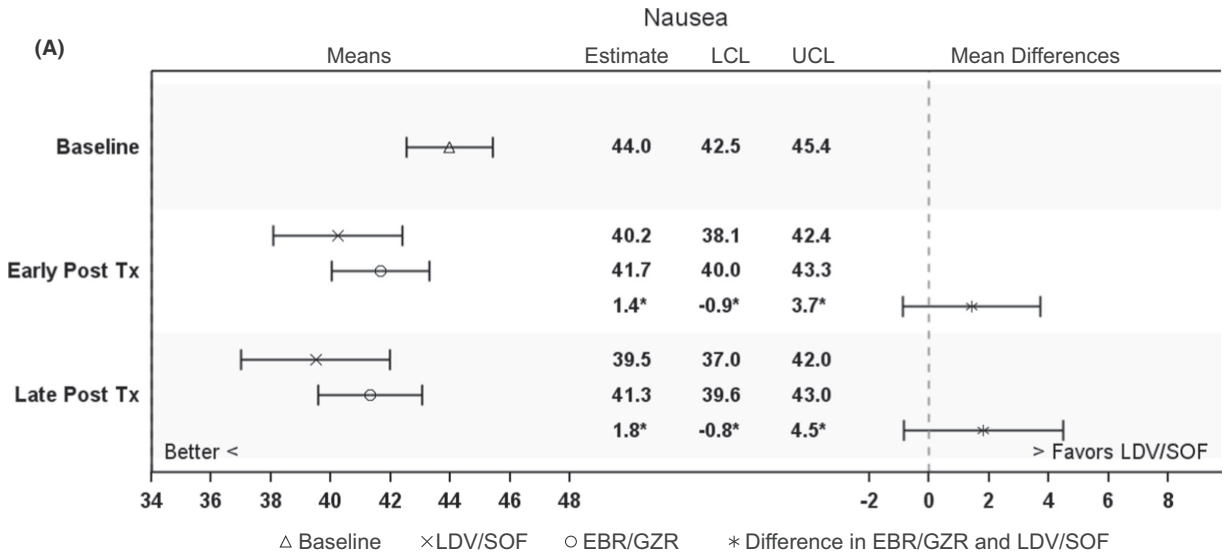


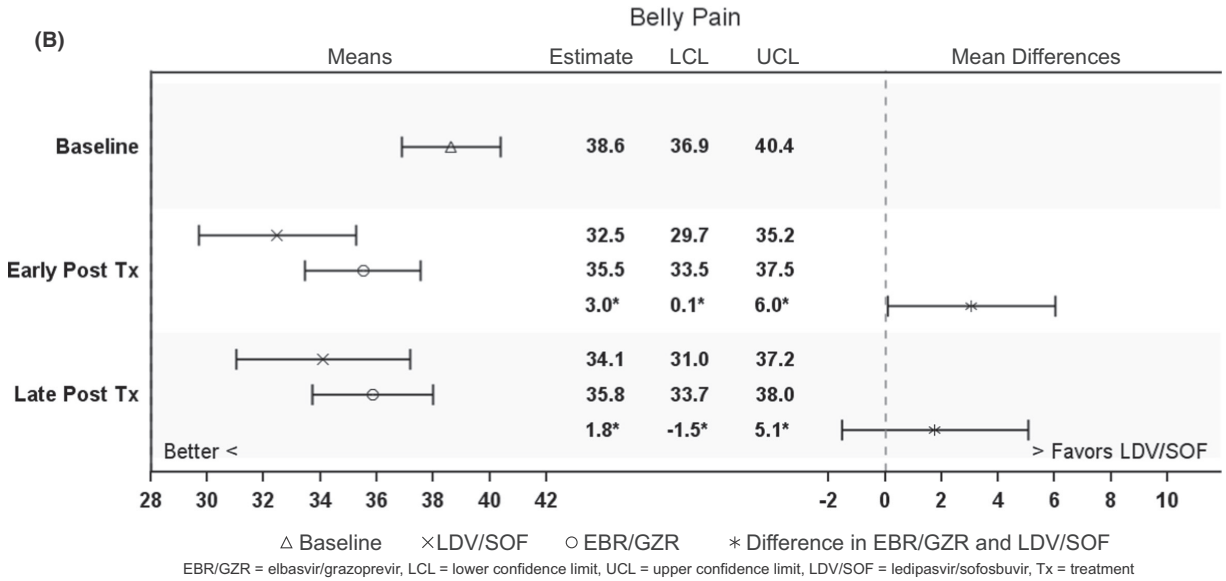
EBR/GZR = elbasvir/grazoprevir, LCL = lower confidence limit, UCL = upper confidence limit, LDV/SOF = ledipasvir/sofosbuvir, Tx = treatment



EBR/GZR = elbasvir/grazoprevir, LCL = lower confidence limit, UCL = upper confidence limit, LDV/SOF = ledipasvir/sofosbuvir, Tx = treatment

FIGURE 2 Fatigue, sleep disturbance and cognitive impairment mean and mean difference estimates for LDV/SOF and EBR/GZR at early and late post-treatment using constrained longitudinal data analysis (cLDA) models, controlling for cirrhosis status, treatment experience, genotype 1 subtype, sex, age, race





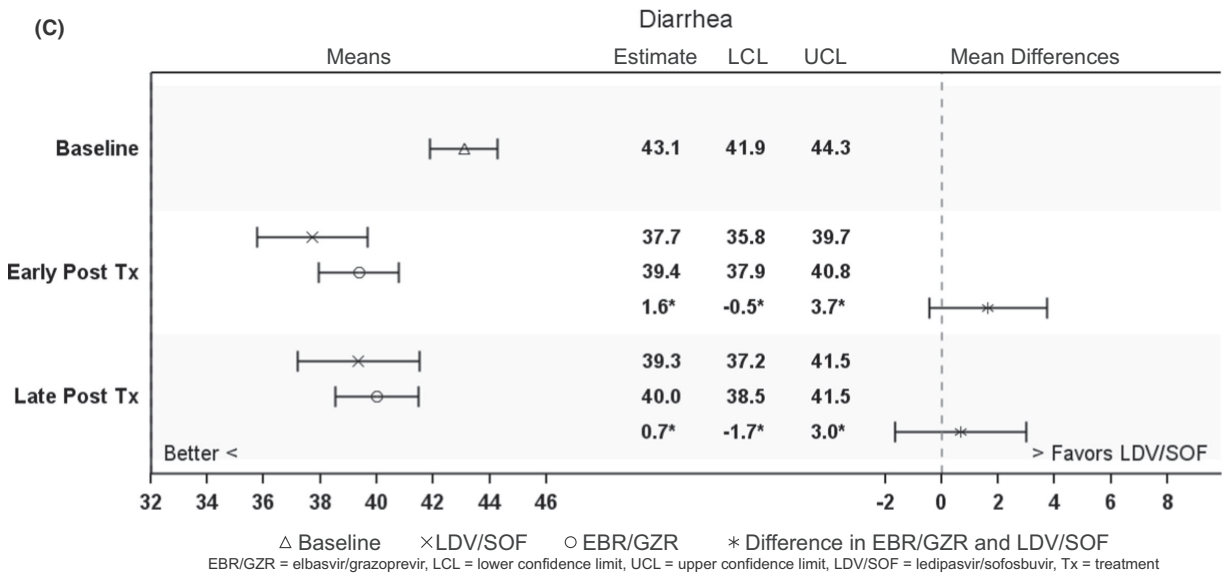


FIGURE 3 Nausea, belly pain, diarrhoea mean and mean difference estimates for LDV/SOF and EBR/GZR at early and late post-treatment using constrained longitudinal data analysis (cLDA) models, controlling for cirrhosis status, treatment experience, genotype 1 subtype, sex, age, race

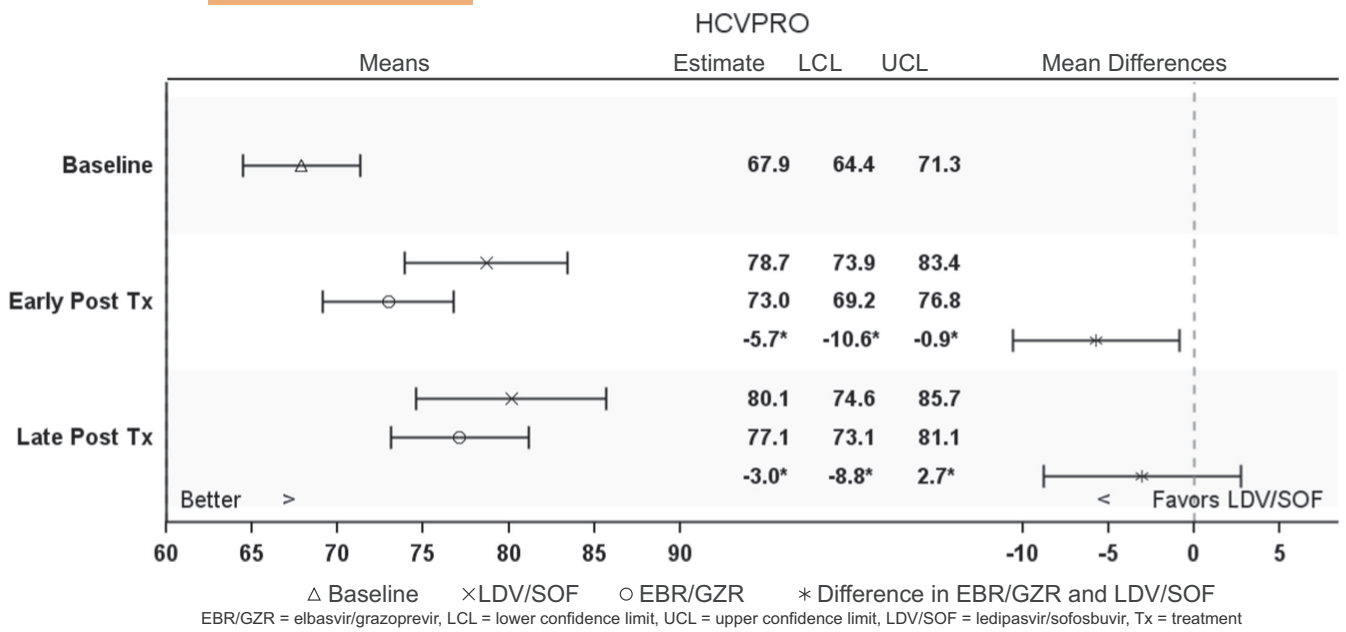


FIGURE 4 HCV-PRO functional well-being mean and mean difference estimates for LDV/SOF and EBR/GZR at early and late post-treatment using constrained longitudinal data analysis (cLDA) models, controlling for cirrhosis status, treatment experience, genotype 1 subtype, sex, age, race

TABLE 3 Between-treatment comparison of EBR/GZR vs. LDV/SOF on changes in symptoms and functional well-being from baseline to post-treatment phases

	Early post-treatment				Late post-treatment			
Concept	**Estimate[t]**	**Lower**	**Upper**	**Pr > |t|**	**Estimate[t]**	**Lower**	**Upper**	**Pr > |t|**
Nausea/Vomiting	1.43	−0.86	3.72	.2220	1.81	−0.84	4.47	.1808
Belly Pain	3.04	0.08	6.00	.0442	1.76	−1.55	5.06	.2970
Diarrhoea	1.64	−0.45	3.73	.1247	0.67	−1.67	3.00	.5755
Fatigue	1.75	−0.95	4.45	.2041	2.09	−1.04	5.22	.1908
Sleep Disturbance	0.57	−1.05	2.18	.4900	0.30	−1.51	2.11	.7418
Cognitive Impairment	1.82	−0.26	3.91	.0869	−0.07	−2.40	2.26	.9531
HCV-PRO	−5.72	−10.58	−0.86	.0211	−3.03	−8.77	2.71	.3004

Note: [t]Point estimates and 95% confidence intervals of mean difference for each symptom between EBR/GZR and LDV/SOF. Positive numbers suggest greater symptom improvement in LDV/SOF arm. Negative numbers for HCV-PRO suggest greater improvement in LDV/SOF. Symptoms were assessed by PROMIS instruments.

different treatment regimens in order to make the most informed treatment decisions.

AUTHOR CONTRIBUTIONS

Donna Evon, Meichen Dong, Joy Peter, Larry Michael, Anna Lok, David Nelson and Paul Stewart performed the research; Donna Evon, Meichen Dong, Joy Peter, Larry Michael, Anna Lok, David Nelson and Paul Stewart collected and analysed the data; Donna Evon, Meichen Dong, Bryce Reeve, Joy Peter, Anna Lok, David Nelson and Paul Stewart designed the research study and wrote the paper; Donna Evon, Bryce Reeve, Joy Peter, David Nelson and Paul Stewart contributed to the design of the study. All authors have approved the final version of the article, including the authorship list.

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CONFLICTS OF INTERESTS

Bryce Reeve was a paid consultant for the University of Florida for his effort on the PRIORITIZE study. Donna Evon has received research funding from Gilead and Merck (paid to the University of North Carolina). David Nelson and Joy Peter own shares in Target Pharma Solutions. Meichen Dong, Larry Michael, Anna Lok and Paul Stewart have nothing to disclose.

DATA AVAILABILITY STATEMENT

Data available upon request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

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