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A Pragmatic, Randomized Controlled Trial of Oral Antivirals for the Treatment of Chronic Hepatitis C: THE PRIORITIZE STUDY

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Abbreviations: Direct-acting antiviral (DAA); Hepatitis C virus (HCV); Ledipasvir (LDV); Sofosbuvir (SOF); United States (U.S.); Elbasvir (EBR); Grazoprevir (GZR); Paritaprevir/ritonavir/ombitasvir+dasabuvir (PrOD); Sustained viral response at 12 weeks (SVR12); Confidence-interval (CI); Patient-Centered Outcomes Research Institute (PCORI); World Health Organization (WHO); Adverse events (AEs); Ribavirin (RBV); Research Data-Capture (REDCap); Child-Turcotte-Pugh (CTP); Resistance-associated substitutions (RASs); Medical Dictionary for Regulatory Activities (MeDRA); Patient-reported outcome (PRO); Headache Impact Test (HIT); Patient-Reported Outcomes Measurement Information System® (PROMIS®); Voils Medication Adherence Survey (VMAS); International Committee of Medical Journal Editors (ICMJE); Modified intent-to-treat (mITT); Heterogeneity of treatment effects (HTE); Least absolute shrinkage and selection operator (LASSO); Constrained longitudinal data analysis (cLDA); Hepatitis B virus (HBV);

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ABSTRACT

Background & Aims: Multiple direct-acting antiviral (DAA) regimens are available to treat hepatitis C virus (HCV), genotype 1 infection. However, comparative effectiveness from randomized controlled trials of DAA regimens is unavailable.

Approach & Results: We conducted a pragmatic randomized controlled trial (NCT02786537) to compare the effectiveness of DAAs for HCV genotype 1a or 1b on viral response, safety, tolerability, and medication non-adherence. Adults with compensated liver disease, HCV genotype 1, not pregnant or breast feeding, and with health insurance likely to cover ledipasvir/sofosbuvir (LDV/SOF) were recruited from 34 U.S. viral hepatitis clinics. Participants were randomized ($\pm$ ribavirin) to ledipasvir/sofosbuvir (LDV/SOF), elbasvir/grazoprevir (EBR/GZR), and paritaprevir/ritonavir/ombitasvir+dasabuvir (PrOD; treatment arm stopped early). Primary outcomes included sustained viral response at 12 weeks (SVR12), clinician-recorded adverse events, patient-reported symptoms, and medication non-adherence.

Between June 2016 and March 2018, 1609 participants were randomized. Among 1128 participants who received $\geq$ 1 dose of EBR/GZR or LDV/SOF ($\pm$ ribavirin), SVR12 were 95.2% [95% CI, 92.8 to 97.6] and 97.4% [95% CI, 95.5 to 99.2] respectively, with a difference estimate of 2.2% [-0.5, 4.7%], falling

within the 'equivalence' interval [-5, 5%]. While most (56%) participants experienced adverse events, few were serious (4.2%) or severe (1.8%). In the absence of ribavirin, discontinuations due to adverse events were rare. Patient-reported symptoms and medication non-adherence were similar. Study limitations were drop-out due to insurance denial and lost to follow-up after treatment, limiting the ability to measure SVR12.

Conclusions: This pragmatic trial demonstrated high SVR12 for participants treated with EBR/GZR and LDV/SOF with few adverse effects. Overall, the two regimens were equivalent in effectiveness. The results support current HCV guidelines that do not distinguish between ribavirin-free EBR/GZR or LDV/SOF.

INTRODUCTION

Hepatitis C virus (HCV) chronically infects more than 2.4 million people in the United States (US) and 70 million people globally, placing these individuals at risk for cirrhosis, liver failure, hepatocellular carcinoma, and death.(1) Compared to those with ongoing infection, persons who achieve HCV cure have markedly lower risk of liver disease complications, and the incidence rate of HCV-related death in the US has declined with the uptake of curative HCV treatment.(2) Accordingly, the World Health Organization (WHO) endorsed the elimination of hepatitis C as a public health threat by 2030, which will require the diagnosis and treatment of most people living with HCV and, if achieved, will reduce HCV-related mortality by 65% over the next ten years.(3) In this context, multiple DAA regimens are available for the treatment of hepatitis C including the most common strain in the United States and world, HCV genotype 1.

Recommended DAA regimens for persons who have not been previously treated combine two drugs that target different steps in the HCV life cycle to create effective antiviral regimens, including HCV NS5A inhibitors (elbasvir, ledipasvir, velpatasvir) and NS3 protease inhibitors (grazoprevir) or NS5B polymerase inhibitors (sofosbuvir).(4) Although recommended as first-line therapy for HCV genotype 1 infection, these combinations may have different safety, tolerability and efficacy in some patient subpopulations. Despite the widespread use of these and other DAA regimens, evidence of comparative effectiveness from randomized controlled trials is unavailable.

We conducted a comparative effectiveness study, designed as a randomized, pragmatic clinical trial (The PRIORITIZE Study, NCT02786537) of the effectiveness of three DAA regimens for treatment of HCV genotype 1a or 1b on (1) sustained viral response at 12 weeks post-treatment (SVR12), (2) clinician-

recorded adverse events (AEs), (3) patient-reported symptoms and functional well-being, and (4) patient-reported medication non-adherence.

METHODS

Study design

PRIORITIZE was a multi-center, randomized, pragmatic clinical trial comparing three DAA regimens: ledipasvir/sofosbuvir (LDV/SOF, Harvoni®, Gilead Sciences, Foster City, CA); elbasvir/grazoprevir (EBR/GZR, Zepatier™, Merck and Co, Whitehouse Station, NJ); paritaprevir/ritonavir/ombitasvir + dasabuvir (PrOD, Viekira Pak/Viekira XR™, AbbVie Pharmaceuticals, Abbott Park, IL) (Phase I only). Consistent with prescribing information and guidelines, ribavirin (RBV) could be added to any regimen at the discretion of the treating clinician. Treatment assignment was open label and efficacy outcomes were unblinded.

We planned to randomize 3750 participants in a 1:1:1 ratio. In January 2017, in anticipation of a US guideline (4) recommendation that PrOD +RBV was to become non-preferred for genotype 1a infection, randomization to PrOD was discontinued (defining the end of Phase 1).   In Phase 2, enrollees were randomized 1:1 to LDV/SOF or EBR/GZR.

At the start of Phase 2, a blinded update of the sample size estimation accounted for the loss of one arm and the low prevalence (~ 15%) of cirrhosis in Phase 1. The revised enrollment target was 1600 enrolled participants. In both phases, randomization was stratified by cirrhosis status and genotype 1 subtype (a or b). This report is limited to outcomes from LDV/SOF and EBR/GZR in phases 1 and 2. Since the regimen was discontinued in the United States and no longer recommended in other regions, comparisons to PrOD in phase 1 are available in the appendix materials. (**Appendix**)

Study Coordination

The Data Coordinating Center used a Research Data-Capture (REDCap) system to conceal the randomized allocation of treatment assignments, to validate patient eligibility, and to capture and manage the study data. The Clinical Coordinating Center used the operational infrastructure of the HCV-TARGET Research Network (5) for standardized, centralized chart data abstraction and targeted data monitoring. All survey instruments were administered by phone interview or by a secure, web-based link into the REDCap system. Participants received $40 remuneration for completing each survey session.

Recruitment

Adult participants (older than 18 years) with chronic HCV genotype 1a or 1b infection who presented for initial antiviral treatment were invited to participate if, in their clinician's opinion, therapy with any of the study regimens was appropriate. The 34 study sites were selected from those participating in the HCV TARGET network. Site clinicians were generally experienced with the management of patients with chronic HCV infection based on their involvement in HCV TARGET (Supplemental Table 1). Individuals were excluded for inability to provide written informed consent, current or historical evidence of hepatic decompensation (variceal bleeding, hepatic encephalopathy, or ascites) unless this was prior to successful liver transplant, Child-Turcotte-Pugh (CTP) stage B or C cirrhosis, pregnancy, or breastfeeding, or health insurance that did not permit LDV/SOF which was not provided by the study. Individuals with HIV coinfection, organ transplantation, substance use disorder (past or current) and other medical or psychiatric conditions were eligible.

Drug regimens

EBR/GZR was provided with no prior authorization or cost to participants via a centralized pharmacy; LDV/SOF was provided by prescription and, when applicable, subject to insurance authorization procedures performed by clinical site and the Kroger Specialty Pharmacy. Regardless of the source of medication, participants were treated according to standard practice which, while not protocol-mandated, generally followed US prescribing information and HCV guidelines (4). All participants were offered free, real-time testing for the presence of NS5A resistance-associated substitutions (RASs) at amino acid positions 28, 30, 31 and 93 (Laboratory Corporation of America, Burlington, North Carolina). LDV/SOF was administered as one tablet (90/400 mg) daily for 8 or 12 weeks at clinician discretion. EBR/GZR was administered as one tablet (50/100 mg) daily for 12 weeks; participants infected with NS5A-resistant genotype 1a received 16 weeks of EBR/GZR plus twice-daily RBV dosed according to body weight.

Outcome measures

   Effectiveness. The primary outcome was undetectable HCV RNA at 12 weeks after the completion of treatment, a binary indicator of SVR12. Values were missing for participants who did not return for HCV RNA testing, and for randomized participants who did not start treatment.

   Safety and Tolerability. Adverse events (AEs) were defined as any new symptom or event recorded in the medical record regardless of whether it was related to HCV therapy. AEs were further coded according to the Medical Dictionary for Regulatory Activities (MeDRA). Serious AEs were defined as any

AE causing death, requiring hospitalization, or meeting criteria for expedited reporting per FDA. Non-serious AE severity was coded as: mild (requiring no concomitant or only over-the-counter therapies), moderate (requiring prescription therapy or HCV treatment dose adjustment), or severe (requiring HCV therapy discontinuation or blood transfusion). On treatment adverse event causal relationships were coded as "related" to HCV therapy based on contemporaneousness of the event to drug administration unless the event was clearly noted in the submitted medical records as "not related" to the HCV treatment regimen.

Patient-reported outcome (PRO) survey. We collected PROs to evaluate functional well-being and symptoms that have been frequent in phase 3 clinical trials of DAAs, specifically headache, fatigue, and nausea. These were assessed on three occasions: pre-treatment, early on-treatment, and late on-treatment. Headache was evaluated by the Headache Impact Test (HIT-6). (6,7) Fatigue was evaluated via the Patient-Reported Outcomes Measurement Information System® (PROMIS®) Fatigue short form 8a, (8,9) and nausea was assessed with the PROMIS® Nausea/Vomiting 4-item short form. (10,11) The raw scores were transformed to standardized PROMIS® T-scores. Functional well-being was assessed on the same occasions using the HCV-PRO instrument. (12) Based on stakeholder input from the PRIORITZE Patient Engagement Group (PEG) during the study design phase, we did not ask information about active substance use.

Medication Adherence. We used the Voils Medication Adherence Survey (VMAS) (13,14) which asked the participant three questions about the past seven days of treatment (early and late on-treatment occasions). Participants responded using a five-point ordinal scale of missed dosing from 1 (none of the time) to 5 (all the time). On each occasion participants were coded as being non-adherent if any response was > 1.

Statistical Analyses

Our analyses and reporting are consistent with guidance from the CONSORT Statement (15), the American Statistical Association (16,17,18,19), and the International Committee of Medical Journal Editors (ICMJE) (20). The main model-based analysis results are presented in this report as point-estimates and confidence-interval (CI) estimates of population parameters. Intent-to-treat estimation was modified (mITT) due to missing values for enrollees who did not start treatment or did not return for SVR12 evaluations. To cope with missing data we followed the approach of White, et al: (1) attempt to avoid missing data, (2) use non-missing data to perform a main analysis specified *a priori* that is valid under plausible assumptions about causes of missing data, (3) use sensitivity analyses to guide trust in the main results by evaluating their robustness/fragility to reasonable perturbations of assumptions and methods used, (4) account for all randomized enrollees in at least one sensitivity analysis (21). For the main analyses we anticipated and assumed mechanisms that caused missing data are ignorable. In our

sensitivity analyses, baseline characteristics of all randomized enrollees played an important role in our investigation of potential selection biases, e.g., we used inverse-probability weighting, multiple imputation of outcomes, as-treated analyses, and variations on model assumptions. In the main analyses, we modeled the assigned DAA regimen, cirrhosis status, genotype 1 subtype, and specified covariates (sex, age-group, treatment naïve status, race) along with terms representing interactions of regimen with cirrhosis, sub-genotype, and race.

SVR12 effectiveness. Due to the small number of participants not achieving SVR12, the main logistic regression model for effectiveness represented the probability of achieving SVR12 as a function of just three variables: assigned DAA regimen, cirrhosis status, and subtype. Fitted using Firth's penalized likelihood method, (22) this model provided point- and interval-estimates of the regimen-specific proportions (P_1, P_2) and their difference (P_1-P_2) in the target population. We performed a superiority test of the null hypothesis "(P_1-P_2) = 0 in the target population" and an equivalence test of the null hypothesis "$|P_1$-$P_2| \geq 5\%$ in the target population".   It is plausible that both null hypotheses are false (i.e., $0\% < |P_1$-$P_2| < 5\%$). For hypothesis generation regarding heterogeneity of treatment effects (HTE), (1) covariates were added to the model one-at-a-time to avoid over-fitting bias, (2) an over-fitted logistic model with LASSO penalized likelihood estimation was explored, and (3) unadjusted SVR12 frequencies for subgroups were examined.

Safety and Tolerability.   Clinically recorded AEs, laboratory abnormalities, and reasons for discontinuation were tabulated for each regimen 'as-treated'.

Patient-reported outcomes.   To characterize and compare the regimens, we used a linear mixed-effects model to estimate means and mean changes from baseline to on-treatment for each of four PRO measures: HIT-6 score, PROMIS® fatigue T-score, PROMIS® nausea T-score, and HCV-PRO. In these constrained longitudinal data analysis (cLDA) models (23), the baseline score was treated as one of the longitudinal outcomes and mean response was represented as a function of as-randomized regimen and the *a priori* covariates and interactions described above. Therefore, an on-treatment mean increase from baseline would be evidence of participants becoming more symptomatic during treatment. The models were also used to explore subgroup differences and HTE. Sensitivity analyses included analysis of residuals, comparison to analyses that used inverse-probability-of-missing weighting or did not assume treatment assignment had no effect on scores at baseline.

Medication non-adherence. We used a generalized logistic regression model for repeated binary measures, which represented the probability of patient-reported non-adherence as a function of regimen, cirrhosis status, genotype, and VMAS survey occasion (early, late) during treatment. As-treated and as-randomized (mITT) treatment effects were estimated separately. Point- and interval-

estimates of population proportions (P_1, P_2) and difference (P_1-P_2) were obtained and a superiority test was conducted.

Non-Adherence and SVR12. For hypothesis generation about potential association between the rare cases of non-SVR12 and rare cases of medication non-adherence, we examined frequencies and obtained point- and interval- estimates of the Pearson correlation coefficient.

Informed consent

This study complied with the U.S. Department of Health and Human Services Federal Policy for the Protection of Human Research Subjects. It relied on National Institutes of Health interpretation of the Common Rule. The study observed site institutional review board and federal requirements for protection of human subjects and their health information. All participants provided written informed consent before screening for enrollment.

Role of the funding sources

RESULTS

Between June 2016 and March 2018, 1609 participants were enrolled at 34 US centers. Of these randomized participants, 1128 received at least 1 dose of EBR/GZR (n=700) or LDV/SOF (n=428) **(Figure 1)** and were followed longitudinally. Failure to initiate therapy was more frequent among participants randomized to LDV/SOF (41%, 298 of 726 participants) than EBR/GZR (4%, 29 of 729 participants). Of the 726 enrollees randomized to LDV/SOF, 150 (21%) experienced insurance denial of treatment and another 168 (23%) did not start for diverse reasons – including the burden of the prior authorization process; 408 were treated with LDV/SOF, and 20 (with insurance denials) were treated with EBR/GZR. Insurance denials of LDV/SOF were primarily by state Medicaid programs (75% of the 150 denials) [30]. The 1128 treated participants were more commonly men (60%) than women (40%); the mean age was 55 years, approximately 42% were Black, 17% had cirrhosis and 3% had HIV co-infection. NS5A resistance associate substitutions (RASs) at key amino acid positions (28, 30, 31, or 93) were detected in 9.9% and 12.6% of participants receiving EBR/GZR and LDV/SOF, respectively. Ribavirin was co-administered was more frequently with EBR/GZR (56 participants, 8%) compared to LDV/SOF (15 participants, 3.5%) (**Table 1**). Of the 1128 participants who began treatment, 91% completed therapy and 85% returned for SVR12 evaluation with similar proportions for each DAA regimen. The proportion

of participants lost to follow-up was ~ 16% for both regimens (LDV/SOF, n=69, 16.1% and EBR/GZR, n=114, 16.3%). Discontinuation due to adverse events (n=22) or lack of efficacy (n=1) was rare.

SVR12 Effectiveness

Primary results.   In the modified intention-to-treat analysis, the adjusted proportions (adjusted for cirrhosis and genotype) who achieved SVR12 for EBR/GZR and LDV/SOF were 95.2% [92.8, 97.6%] and 97.4% [95.5, 99.2%] respectively. The difference of 2.2% [-0.5, 4.7%] was within the pre-specified equivalence range [± 5%]. The superiority test was inconclusive (p=0.0930). Among the 945 participants with known SVR12 outcomes, only 40 (4.2%) did not achieve SVR12 including 5.1% (30 of 586 participants; non-response, 11, relapse, 18, breakthrough, 1) and 2.7% (10 of 359 participants; non-response, 10; relapse, 7) of those randomized to EBR/GZR and LDV/SOF, respectively (Supplemental Table 2).

Exploratory results.   Exploratory analyses of heterogeneity of treatment effect based on unadjusted SVR12 proportions (**Table 2**) suggested the following: 1) SVR12 proportions were similar for Black and non-Black participants treated with EBR/GVR and LDV/SOF; 2) Participants with NS5A RASs treated with either DAA regimen may have lower SVR12 proportions compared to those without NS5A RASs; the difference was 9.3% [-0.3, 18.2%] for LDV/SOF, and 8.8% [-0.3, 7.9%] for EBR/GZR. The SVR12 rate for patients with specific NS5A RASs at positions 28, 30, 31, and 91 are presented by DAA regimen in Supplemental Table 3a (patients with HCV genotype 1a infection) and 1b (patients with HCV genotype 3b infection); 3) Among women, the SVR12 proportions between DAA regimens differed by 5.1% [95% CI 2.4, 7.7%] in favor of LDV/SOF; 4) Among participants with genotype 1a infection, the SVR12 proportions between DAA regimens differed by 3.5% [95% CI 0.1, 6.4%] favoring LDV/SOF, 5) The difference is SVR between regimens among non-cirrhotic participants was 3.4% [95% 0.5, 6.1%] favoring LDV/SOF; whereas, among those with cirrhosis the difference was -2.8% [95% CI -11.5, 4.0%] favoring EBR/GZR.

Safety and tolerability

The percentage of participants treated with EBR/GZR or LDV/SOF with any adverse event was 56% (628 of 1129 participants). Among those patients experiencing any adverse event, most had AEs coded as related to HCV treatment (601 of 628 patients with adverse events). Participants taking DAAs plus ribavirin reported more adverse events than those not taking DAAs alone. The most common AEs recorded in the medical record were fatigue (19%), headache (16%), and nausea (9.1%). Anemia (27%), dizziness (10%) and insomnia (10%) were observed almost exclusively in participants prescribed RBV. Severe AEs were observed in 1.8% (n=23) of 1129 participants. Serious AEs occurred in 4.2% (42

participants with 53 events), of which two were considered treatment-related, chest pain and flare of hepatitis B virus (HBV) infection.

Liver-related adverse events were rare, occurring in 7 patients (0.6%) with 8 events (0.4%) among 1129 participants. Hepatic decompensation was not observed in the 102 participants with cirrhosis who received the HCV protease inhibitor, grazoprevir (part of the EBR/GZR regimen); however, one non-cirrhotic patient treated with EBR/GZR had HBV reactivation with evidence of trace ascites. Early discontinuation of treatment due to an adverse event occurred in 22 participants and the incidence was similar in participants treated with LDV/SOF (7 of 409, 1.7%) and EBR of GZR (15/720, 2.1%). Six participants treated with EBR/GZR or LDV/SOV died during the study, with 5 deaths during treatment; none were treatment related.

Patient-reported outcomes

In terms of mean changes in patient-reported outcomes from baseline, symptoms did not worsen and during treatment with either regimen and the mean scores for measures of symptoms (headache, nausea and fatigue) and overall functioning and well-being improved during treatment relative to baseline (**Figure 2**). For functional well-being, the difference favored LDV/SOF: -4.3 [-8.4, -0.3]; p=0.0354.

Medication Non-Adherence.

Treatment persistence was high for both regimens; 90% of EBR/GZR treated participants and 92% of LDV/SOF treated participants completed the planned duration of therapy. The difference of 2% [-1.5, 5.4] did not favor either regimen. The regimens were similar in the as-treated estimates of non-adherence: 16% [1, 21%] for LDV/SOF, 20% [12, 23%] for EBR/GZR (p=0.20).   In models controlling for treatment duration and other factors, there was no evidence of an effect of treatment duration on the probability of adherence. These comparisons indicate little or no difference in adherence or persistence for patients prescribed LDV/SOF or EBR/GZR.   The proportion of participants who achieved SVR12 was independent of adherence. (**Appendix**)

Sensitivity analyses

We found negligible impact of patient drop-out (failure to start treatment, or failure to return after treatment) based on estimates obtained using inverse probability of missing weighting, and estimates

using multiple imputation of SVR12 values. The results of other sensitivity analyses of patient reported outcomes and non-adherence closely approximated the main results.

DISCUSSION

This pragmatic trial is the first comparative effectiveness study for oral direct acting antivirals for the treatment of chronic HCV infection. We treated 1128 participants with genotype 1 infection at 34 clinical sites in the United States and randomly assigned them to one of two recommended antiviral regimens. Consistent with observations from efficacy trials and clinical cohorts, SVR12 proportions were high for both DAA regimens (≥ 95%) and HCV virologic failure was uncommon (<1%). In the absence of ribavirin, the DAA regimens had similar side-effect profiles based on the medical records and treated participants reported improved symptoms and functional well-being during and after therapy. These findings have important implications for the treatment of HCV infection, globally and by non-specialists, since the safety and tolerability of ribavirin-free regimens allows for minimal monitoring during therapy.

The randomized design of our study allowed for direct comparison of the effectiveness and side effect profile of these two recommended DAA regimens, EBR/GZR and LDV/SOF. The overall SVR12 proportions were similar, with strong evidence that the two regimens are equivalent in the target population. Compared to the registration trial enrollment for these regimens (EBR/GZR, 18% and LDV/SOF, 12 to 15%), we enrolled a significantly larger proportion of Black Americans. Approximately, 42% of the PRIORTIZE study populations was Black allowing for greater precision around the estimated SVR12 rate, which was similar for both DAA regimens and the SVR observed in non-Black participants. The high participation rate in the study by Black Americans, a group underrepresented in HCV trials, also provides a roadmap for continued engagement to reduce HCV-related disparities and health inequities, essential for the elimination of hepatitis C as a public health threat. (24,25)

We also observed small differences in the unadjusted SVR12 proportions in important patient subgroups in exploratory analyses conducted for hypothesis generation. For both EBR/GZR and LDV/SOF, the SVR12 rate was lower in participants with NS5A resistance-associated substitutions compared to those with wild-type HCV. Since only 1 in 10 patients had evidence of baseline NS5A resistance and the impact of SVR was similar for both DAA regimens, we do not believe that our data support routine RAS testing prior to therapy. We also observed small differences in the unadjusted SVR12 proportions favored LDV/SOF in women, in those with genotype 1a infection, and in those without cirrhosis. Conversely, these small differences in the unadjusted SVR12 proportions favored EBR/GZR in participants with cirrhosis. These exploratory observations are consistent with reports from uncontrolled trials of each

regimen and may serve to guide the selection of HCV treatment regimen by patients and clinicians. (26,27,28,29)

Overall, 56% of participants experienced some adverse events during treatment but few were severe (1.8%) or serious (3.7%) and few participants (< 2%) discontinued ribavirin-free treatment due to an AE. As expected, participants who received ribavirin experienced more AEs unique to ribavirin use. Clinical and laboratory abnormalities were uncommon with ribavirin-free DAAs with few treatment-related serious AEs including liver related events in persons taking HCV protease inhibitors, which has been associated with liver dysfunction and death in participants with moderate to severe liver impairment. (30) In our study population, which did not include persons with decompensated cirrhosis, liver related adverse events were rare. We also measured patient reported outcomes with surveys to evaluate changes in headache, nausea, and fatigue from baseline, demonstrating that, on average, these symptoms did not worsen during either treatment regimen, consistent with previous studies of PROs. (31) Similarly, functional well-being improved on average during treatment with both regimens and especially in participants receiving LDV/SOF.

Our study findings should be interpreted in the context of several limitations: (1) Due to the economic barriers in accessing HCV treatment in the US at the time of this study, we provided participants with EBR/GZR sourced directly from commercial manufacturer, whereas LDV/SOF was sourced externally via commercial or other health insurance. As a result of health insurance denial and other barriers to treatment access (e.g., prior authorization), failure to start treatment was more common in participants randomized to LDV/SOF resulting in some imbalances in patient characteristics between the treatment arms. (32) Despite this, our sensitivity analyses indicated that these occurrences of pre-treatment drop-out (as well as the post-treatment drop-outs) did not induce selection biases. Further, the observation that curative treatment was denied to 41% of patients using health insurance underscores the impact of systemic barriers to HCV elimination. (2) The HCV treatment landscape changed rapidly during our study, leading to discontinuation of one arm (PrOD) and modification of our research plans. (3) Several factors (e.g., declining prevalence of cirrhosis and lost to follow-up during and after treatment) limited the number of non-SVR12 cases to a level (n=40) that did not support our intended investigation of the heterogeneity of treatment effect across subgroups. To avoid over-fitting bias, the logistic model for SVR12 analysis was limited to accounting for only three factors: regimen, cirrhosis, genotype 1 subtype and inclusion of subgroup-by-treatment interaction terms was not feasible. (4) Based on feedback from patient stakeholders during the study design phase, we did not collect data related to active substance use which precludes analysis. (5) We were not able to evaluate

the two newer, pangenotypic regimens, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir as they were not available at the time of the study.

The PRIORITIZE study is the first, large randomized controlled trial to compare oral DAA regimens for the treatment of chronic HCV infection on effectiveness, safety, side effects, and medication adherence in a usual clinical-care setting. Our findings are consistent with observations from controlled phase III efficacy trials and uncontrolled cohort studies, demonstrating high SVR12 proportions with few virologic failures, and in the absence of ribavirin, minimal adverse effects. Our data support HCV guidelines that do not distinguish between ribavirin-free EBR/GZR or LDV/SOF for the treatment of persons with compensated liver disease due to HCV genotype 1 infection. While this trial had a large, representative population there was a low proportion of patients with cirrhosis and no patients with decompensated cirrhosis. Findings may not generalize to the larger HCV population including decompensated cirrhosis, younger people injecting drugs, Veterans, and those incarcerated.

Future randomized controlled trials should focus on the comparative effectiveness of the recommended pangenotypic DAA regimens, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir.

Figure Legends

Figure 1. Consort diagram – PRIORITIZE Study Flowchart

Figure 2. Mean Change in PRO Scores from Baseline to On-Treatment

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Table 1. Baseline characteristics of treated participants as randomized to EBR/GZR and LDV/SOF

	EBR/GZR	LDV/SOF
Participants who started treatment	700	428
Age, years mean (range)	53.4 (18.0-83.0)	56.4 (21.0-82.0)
Sex n (%)		
Female	293 (41.9)	163 (38.1)
Male	407 (58.1)	265 (61.9)
Race n (%)		
White	349 (49.9)	225 (52.6)
Black	295 (42.1)	182 (42.5)
Other	56 (8.0)	21 (4.9)
HCV GT1 Subtype n (%)		
1a	540 (77.1)	317 (74.1)
1b	160 (22.9)	111 (25.9)
Cirrhosis n (%)		
yes	112 (16.0)	80 (18.7)
no	588 (84.0)	348 (81.3)
NS5A RAS n (%)		
RAS at any 28/30/31/93	69 (9.9)	54 (12.6)
RAS at 28 only	28 (4.0)	14 (3.3)
RAS at 30 only	4 (0.6)	2 (0.5)
RAS at 31 only	8 (1.1)	14 (3.3)
RAS at 93 only	21 (3.0)	14 (3.3)
Ribavirin administration n (%)		
yes	56 (8.0)	15 (3.5)
no	644 (92.0)	413 (96.5)
HIV co-infection n (%)		
yes	22 (3.1)	13 (3.0)
Hepatocellular carcinoma history		
yes	4 (0.6)	2 (0.5)
Type of health insurance n (%)		
Medicaid	331 (47.3)	113 (26.4)
Medicare	98 (14.0)	90 (21.0)
Commercial	231 (33.0)	186 (43.5)
Other	40 (5.7)	39 (9.1)
Platelets (1000/ml) mean (range)	222 (39.0-645.0)	216 (67.0-343.0)
Duration of Therapy n (%)		
8 wks (42 days to 69 days)	28 (4)	110 (26)
12wks (70 days-97 days)	562 (80)	275 (64)
16wks (98 days-125 days)	78 (11)	9 (2.1)
Other Durations	32 (4.5)	34 (7.9)
Alcohol/Tobacco Use n (%)		
Current	245(35.0)/348(49.7)	159(37.1)/168(39.3)
Former	166(23.7)/193(27.6)	99(23.1)/150(35.0)
Never	265(37.9)/134(19.1)	157(36.7)/94(22.0)
Unknown	24(3.4)/26(3.6)	13(3.0)/16(3.7)

Of the 428 randomized to LDV/SOF, 20 experienced insurance denial and were then treated with EBR/GZR instead. HCV = hepatitis C virus, RAS = NS5A resistance-associated substitutions, EBR/GZR = elbasvir/grazoprevir, LDV/SOF = ledipasvir/sofosbuvir.

Table 2. Exploratoration of subgroup differences based on unadjusted SVR12 frequencies

Sub-population	Counts	EBR/GZR[1] Percentage (CI)	Counts	LDV/SOF[1] Percentage (CI)	EBR/GZR vs. LDV/SOF Difference (CI)
Overall	**556/586**	**94.9 [92.8, 96.5][2]**	**349/359**	**97.2 [94.9, 98.7]**	**-2.3 [-4.8, 0.4]**
With RBV	40/46	80.7 [73.7, 95.1]	14/15	93.3 [68.1, 99.8]	-6.4 [-20.1, 17.8]
Without RBV	516/540	95.6 [93.5, 97.1]	335/344	97.4 [95.1, 98.8]	-1.8 [-4.2, 0.9]
Black	253/266	95.1 [91.8, 97.4]	153/159	96.2 [92.0, 98.6]	-1.1 [-5.0, 3.6]
Non-black	303/320	94.7 [91.6, 96.9]	196/200	98.0 [95.0, 99.5]	-3.3 [-6.6, 0.3]
Prior treatment	56/62	90.3 [80.1, 96.4]	44/45	97.8 [88.2, 99.9]	-7.5 [-17.5, 3.2]
No prior treatment	500/524	95.4 [93.3, 97.0]	305/314	97.1 [94.6, 98.7]	-1.7 [-4.2, 1.2]
Male	312/329	94.8 [91.9, 96.7]	212/222	95.5 [91.9, 97.5]	-0.7 [-4.3, 3.4]
Female	244/257	94.9 [91.5, 97.0]	137/137	100 [97.3, 100]	-5.1 [-7.7, -2.4]
Genotype 1a	419/445	94.2 [91.6, 96.0]	254/260	97.7 [95.1, 98.9]	-3.5 [-6.4, -0.1]
Genotype 1b	137/141	97.2 [92.9, 98.9]	95/99	96.0 [90.1, 98.4]	1.2 [-3.7, 7.3]
Cirrhosis	92/95	96.8 [91.0, 99.3]	63/67	94.0 [85.4, 98.3]	2.8 [-4.0, 11.5]
No Cirrhosis	464/491	94.5 [92.1, 96.3]	286/292	97.9 [95.6, 99.2]	-3.4 [-6.1, -0.5]
NS5a RAS	47/54	87.0 [75.1, 94.6]	42/47	89.4 [76.9, 96.5]	-2.3 [-15.3, 11.3]
No NS5a RAS	485/506	95.8 [93.7, 97.4]	286/290	98.6 [96.5, 99.6]	-2.8 [-5.0, -0.2]

1 As assigned by randomization

2 95% Confidence Intervals (CI) were computed via the Wilson score method

Trt=treatment

Table 3. All Adverse Events With Prevalence Exceeding 10% By Treatment Regimen[1]

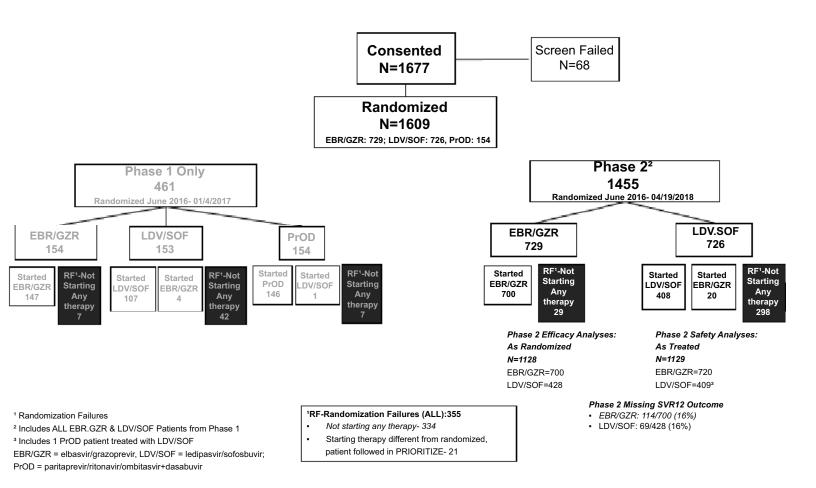|	EBR/GZR			LDV/SOF			OVERALL		
	RBV	No RBV	ALL	RBV	No RBV	ALL	RBV	No RBV	ALL
	(56)	(664)	(720)[2]	(15)	(394)	(409)[3]	(71)	(1058)	(1129)
N Patients-*any AE*	46 (82%)	361 (54%)	407 (57%)	8 (53%)	213 (54%)	221 (54%)	54 (76%)	574 (54%)	628 (56%)
Fatigue	18 (32%)	105 (16%)	123 (17%)	5 (33%)	82 (21%)	87 (21%)	23 (32%)	187 (18%)	210 (19%)
Headache	12 (21%)	94 (14%)	106 (15%)	1 (6.7%)	68 (17%)	69 (17%)	13 (18%)	162 (15%)	175 (16%)
Nausea	12 (21%)	54 (8.1%)	66 (9.2%)	3 (20%)	34 (8.6%)	37 (9.0%)	15 (21%)	88 (8.3%)	103 (9.1%)
Insomnia	6 (11%)	26 (3.9%)	32 (4.4%)	1 (6.7%)	10 (2.5%)	11 (2.7%)	7 (9.9%)	36 (3.4%)	43 (3.8%)
Dizziness	7 (13%)	15 (2.3%)	22 (3.1%)	0 (0%)	11 (2.8%)	11 (2.7%)	7 (9.9%)	26 (2.5%)	33 (2.9%)
Dyspnea	8 (14%)	9 (1.4%)	17 (2.4%)	0 (0%)	11 (2.8%)	11 (2.7%)	8 (11%)	20 (1.9%)	28 (2.5%)
Anemia	17 (30%)	2 (0.3%)	19 (2.6%)	2 (13%)	0 (0%)	2 (0.5%)	19 (27%)	2 (0.2%)	21 (1.9%)
Diarrhea	3 (5.4%)	45 (6.8%)	48 (6.7%)	2 (13%)	19 (4.8%)	21 (5.1%)	5 (7.0%)	64 (6.0%)	69 (6.1%)

[1]As Treated Population

[2] Includes 20 patients randomized to LDV/SOF and treated with EBR/GZR

[3]Includes one patient randomized to PrOD and treated with LDV/SOF

Treatment emergent AEs from treatment start to ≤ 31 days post EOT

AE= adverse event, EBR/GZR = elbasvir/grazoprevir, LDV/SOF = ledipasvir/sofosbuvir, PrOD= paritaprevir/ritonavir/ombitasvir + dasabuvir, RBV=Ribavirin

Consented N=1677 — **Screen Failed N=68**

Randomized N=1609
EBR/GZR: 729; LDV/SOF: 726, PrOD: 154

Phase 1 Only 461
Randomized June 2016- 01/4/2017

EBR/GZR 154
- Started EBR/GZR 147
- RF[1]-Not Starting Any therapy 7

LDV/SOF 153
- Started LDV/SOF 107
- Started EBR/GZR 4
- RF[1]-Not Starting Any therapy 42

PrOD 154
- Started PrOD 146
- Started LDV/SOF 1
- RF[1]-Not Starting Any therapy 7

Phase 2[2] 1455
Randomized June 2016- 04/19/2018

EBR/GZR 729
- Started EBR/GZR 700
- RF[1]-Not Starting Any therapy 29

LDV.SOF 726
- Started LDV/SOF 408
- Started EBR/GZR 20
- RF[1]-Not Starting Any therapy 298

Phase 2 Efficacy Analyses:
As Randomized
N=1128
EBR/GZR=700
LDV/SOF=428

Phase 2 Safety Analyses:
As Treated
N=1129
EBR/GZR=720
LDV/SOF=409[3]

Phase 2 Missing SVR12 Outcome
- *EBR/GZR: 114/700 (16%)*
- LDV/SOF: 69/428 (16%)

[1] Randomization Failures
[2] Includes ALL EBR.GZR & LDV/SOF Patients from Phase 1
[3] Includes 1 PrOD patient treated with LDV/SOF
EBR/GZR = elbasvir/grazoprevir, LDV/SOF = ledipasvir/sofosbuvir;
PrOD = paritaprevir/ritonavir/ombitasvir+dasabuvir

[1]RF-Randomization Failures (ALL):355
- *Not starting any therapy- 334*
- Starting therapy different from randomized, patient followed in PRIORITIZE- 21

hep_32053_f1.eps

		Estimate[1]	95% CI[2]		p-value[3]
Headache	EBR/GZR	−1.17	−1.99	−0.34	0.0057
	LDV/SOF	−1.10	−2.20	0.01	0.0530
	Difference[4]	0.07	−1.04	1.18	0.9001
Nausea	EBR/GZR	−0.38	−2.01	1.25	0.6450
	LDV/SOF	−2.48	−4.63	−0.34	0.0235
	Difference[4]	−2.10	−4.28	0.08	0.0586
Fatigue	EBR/GZR	−1.77	−3.42	−0.12	0.0358
	LDV/SOF	−3.76	−5.97	−1.56	0.0008
	Difference[4]	−1.99	−4.25	0.26	0.0827
Overall Functioning and well being[5]	EBR/GZR	−4.47	−7.51	−1.44	0.0040
	LDV/SOF	−8.80	−12.81	−4.78	<.0001
	Difference[4]	−4.32	−8.35	−0.30	0.0354

← Better[6]   Worse →

−15 −12 −9 −6 −3 0 3

[1] The estimates of mean change and difference were obtained from a constrained longitudinal linear mixed-effects model that treated the baseline score as one of the outcomes. The model expressed mean score as a function of DAA regimen, cirrhosis status, HCV genotype, sex, age, race, and previous treatment status.

[2] 95% confidence interval estimate

[3] p-value for a test of the null hypothesis "the parameter is zero in the target population"

[4] Difference of the mean change for LDV/SOF minus the mean change for EBR/GZR

[5] The scale for function and well-being is reversed (= 100-HCV-PRO) for directional consistency with symptom scores

[6] The scare for "Headache" is the HIT-6 score. The scare for "Nausea" is the PROMIS® Nausea Short Form T-score. The scale for "Fatigue" is the PROMIS® Fatigue Short Form T-score. Negative values for mean change represent improvement, while negative values for "Difference" indicate the LDV/SOF performed better than EBR/GZR