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SOFOSBUVIR/VELPATASVIR IMPROVES PATIENT-REPORTED OUTCOMES IN HCV PATIENTS: RESULTS FROM ASTRAL-1 PLACEBO-CONTROLLED TRIAL

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ZMY: Study design, oversight of data analysis, data interpretation, manuscript writing and manuscript approval

MS: Data analysis, data interpretation, manuscript writing and manuscript approval

JF: Study participation, manuscript editing and manuscript approval

SZ: Study participation, manuscript editing and manuscript approval

IJ: Study participation, manuscript editing and manuscript approval

KA: Study participation, manuscript editing and manuscript approval

CH: Study participation, manuscript editing and manuscript approval

FN: Study concept, data interpretation, manuscript writing and manuscript approval

LH: Study concept, data interpretation, manuscript writing and manuscript approval

SH: Study concept, data interpretation, manuscript writing and manuscript approval
ABSTRACT

The new pan-genotypic regimen [sofosbuvir (SOF) and velpatasvir (VEL)] for HCV has been associated with high efficacy. The aim of this study was to assess patient-reported outcomes (PROs) with this regimen. METHODS: The PRO data (CLDQ-HCV, SF-36, FACIT-F, WPAI) came from the ASTRAL-1 study, a multicenter multinational blinded placebo-controlled phase 3 clinical trial of a fixed dose combination of SOF 400 mg and VEL 100 mg for patients with genotype 1, 2, 4, 5, and 6 compared to placebo for 12 weeks. RESULTS: 624 patients received active treatment (618/624 achieved SVR), and 116 received placebo. The baseline PRO scores were similar. By treatment week 4, patients receiving SOF/VEL experienced improvements in general health (on average, +2.3 points), emotional well-being (+3.4), FACIT-F (+1.3), and all domains of CLDQ-HCV (+2.1 to +7.3) (all p<0.005). On the other hand, the only PRO that improved in patients receiving placebo was the worry domain of CLDQ-HCV: +4.6 (p=0.002). By the end of treatment, improvement in PRO scores with SOF/VEL continued, and no improvement was noted in the placebo. Improvement in PROs were also noted 12 and 24 weeks post-treatment: +3.7, on average, in patients with SVR-12 after SOF/VEL vs. -2.6, on average, in the placebo arm (p<0.005). Multivariate analysis showed that treatment-emergent changes in PROs were predicted by receiving SOF/VEL for some summary PRO score (p<0.005). CONCLUSIONS: This placebo controlled trial shows that patients treated with SOF/VEL experience significant improvement of their patient-reported outcomes during treatment and after achieving a sustained virologic response.
INTRODUCTION

In the last few years, there have been tremendous advances in the field of hepatitis C virus (HCV). In particular, there is mounting evidence that HCV is a systemic disease that is associated with both hepatic and extrahepatic manifestations [1-6]. Furthermore, these hepatic and extrahepatic manifestations of HCV can lead to substantial clinical, economic and quality of life burden to the patients and the society [7-8].

In this context, there is compelling data that HCV infection impairs patient-reported outcomes (PROs) such as health-related quality of life (HRQL), fatigue, and work productivity [9-11]. It has also been reported that prior to treatment, PROs in HCV-infected patients could be additionally impaired in the presence of cirrhosis and psychiatric disorders, such as depression and anxiety [12-13]. Furthermore, on-treatment PRO scores are known to be profoundly affected by treatment with regimens that contain interferon-alpha and ribavirin [14-15]. In this context, assessment of PROs is of utmost importance for a number of reasons. First, on-treatment PROs have been reported to be the major drivers of adherence to anti-HCV treatment [16]. In fact, PROs during treatment may explain the gap that is frequently reported between efficacy rates and those reported for the effectiveness of anti-viral treatment in the real world practices [17]. Second, the proportion of variance in PRO scores in patients with HCV which could be accounted for by routine clinical parameters rarely exceeds 15% [18]. Third, PROs are important surrogates for patients’ experience with their disease and its treatment [17]. Combined, these reasons make PROs important endpoints for clinical trials and irreplaceable sources of important information in clinical practice.
Over the last 5 years, development of highly effective and less toxic regimens to treat HCV, has led to SVR rates over 95% [18-28]. The new all-oral direct-acting antivirals (DAA)-based regimens are not only associated with a better side effect profile, but have also been shown to improve PROs during treatment and after achieving SVR [12,17,29-39]. However, since most studies of the new DAA-based regimens were not placebo controlled, it is still necessary to rule out a perception bias that could undermine the reliability of the changes seen in PRO scores during and after successful treatment [40].

Additionally, the DAA-based regimens reported to date are primarily genotype-specific, and some require the use of ribavirin with known side effects which can also cause a moderate impairment of PROs during treatment [29-36]. Thus, the next advance in treatment of HCV has been the development of interferon-free and ribavirin-free regimen with pan-genotypic efficacy. For that purpose, a combination of sofosbuvir (SOF) and velpatasvir (VEL) has been shown to have SVR rates between 95-100% in HCV genotypes 1-6 [41]. Furthermore, this regimen was found to be well-tolerated with an excellent safety profile. The aim of this current study is to report the impact of this pan-genotypic regimen (SOF/VEL) on PROs during treatment and after achieving sustained virologic response, and compare these scores to the PRO scores from patients who were treated with identical placebo.

METHODS
Data were analyzed from the patients participating in the ASTRAL-1 study, a multicenter multinational double blinded placebo-controlled phase 3 clinical trial of SOF/VEL which was conducted in the U.S., Canada, five European countries (UK, France, Germany, Italy, and
Belgium) and Hong Kong in 2014-2015. The study design and results of this trial have been previously reported [41]. In this trial, patients with genotype 1, 2, 4, 5, and 6 HCV infection were randomized (5:1) to receive an all-oral fixed-dose combination of 400 mg SOF/VEL (400/100mg) once daily for 12 weeks, or an identical placebo for the same period of time. Patients with genotype 5 HCV infection were not randomized and were enrolled into the SOF/VEL treatment group only. The selected sample size was based on the target enrollment into the SOF/VEL group of at least 500 patients which would be sufficient to provide 90% power to detect an improvement of at least 5 percentage points in SVR-12 rate from the performance goal of 85%. A 5:1 ratio of active/placebo was employed as a minimum of 100 placebo treated subject was considered necessary to adequately describe the adverse event profile of placebo treatment; with 100 subjects, rare events occurring in 1 subject would have an incidence of 1% [41]. Out of ethical considerations, all ASTRAL-1 placebo patients received 12 weeks of SOF/VEL in the GS-US 342-1446 protocol once the ASTRAL-1 post-treatment week 12 visit was completed.

Adverse events recorded during the study were grouped based on the body system as previously described [30], and only treatment-related adverse events, labeled as such by the investigators, were selected for this analysis. Also, based on the medical history collected at screening for all enrolled participants, for the purpose of this analysis, we selected patients with pre-treatment history of depression or mood disorders, fatigue or asthenia, anxiety or panic disorders, insomnia or sleep disorders, and type 2 diabetes or hyperglycemia.

*Patient-Reported Outcomes*
Patient-reported outcomes were collected as exploratory endpoints in ASTRAL-1. Patients self-administered the four PRO questionnaires/instruments selected for this study [Short-Form-36 (SF-36; the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Chronic Liver Disease Questionnaire-HCV Version (CLDQ-HCV), the Work Productivity Activity Index: Specific Health Problem (WPAI:SHP)] [42-45]. These questionnaires/instruments were self-administered in their native language and were taken at baseline (day 1 of treatment) and then every four weeks while treatment lasted. Patients were blinded to their HCV RNA results at the time of completing the questionnaires. After treatment completion, the PRO instruments were also administered at weeks 4 and 12 follow-up visits regardless of the study arm, and then at week 24 follow-up visit to patients with SVR-12 only.

The four PRO questionnaires used in this study were 1) the Short-Form-36 (SF-36) (includes 8 individual domains - physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), mental health (MH), as well as physical (PCS) and mental (MCS) components summaries) [42]; 2) the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (includes physical (PWB), emotional (EWB), social (SWB) and functional (FWB) domains, and a fatigue scale (FS)) [43]; 3) the Chronic Liver Disease Questionnaire-HCV Version (CLDQ-HCV) (activity/energy, emotional, worry and systemic domains) [44]; and 4) the Work Productivity Activity Index: Specific Health Problem (WPAI:SHP) (assesses impairment in work productivity, including its absenteeism and presenteeism components, and in activities other than work) [45].
Combined together, these instruments measure 25 domain and summary PROs. Additionally, in all instruments, greater score values reflected better health status, except for WPAI:SHP where a greater impairment score would indicate poorer health. Where stated explicitly, for the presentation purposes, we transformed all PROs from their original scales to a universal 0-100 scale.

**Statistical Analysis**

Together with clinico-demographic parameters, the baseline, on-treatment, and post-treatment PROs were compared between those receiving the active treatment and those receiving a placebo using Pearson's chi-square test for independence or Wilcoxon non-parametric test. Also, at all time points, we calculated the changes (decrements or improvements) in the PRO scores with reference to patients' own baseline levels, and used a Wilcoxon sign rank test for matched pairs to identify the changes that were significant. Due to multiple testing, only p-values of 0.005 or less were considered potentially statistically significant.

The association of the treatment regimen (SOF/VEL as opposed to placebo - the reference regimen) with the summary PROs was assessed using mixed linear models. These models were run with time and treatment regimen being included as fixed interacted effects, subject ID being a random effect, and with adjustment for baseline PRO levels and a number of demographic and clinical predictors. Potential clinico-demographic PRO predictors adjusted for in the mixed models were: location (USA vs. non-USA), age, gender, being treatment-naïve (as opposed to having failed a prior anti-HCV treatment), history of psychiatric diseases, cirrhosis, HCV genotype, and type 2 diabetes.
All analyses were run using SAS 9.3 (SAS Institute, Cary, NC). The study was separately approved by each site’s Institutional Review Board.

RESULTS
In ASTRAL-1, N=624 patients received the active treatment, and N=116 were placebo controls. Baseline clinico-demographic parameters of the study sample are shown in Table 1. Patients were, on average, 53.9 ± 10.8 years of age, 59.7% male, 78.6% white, 8.6% black, 9.9% Asian, 37.7% enrolled in the U.S., and 64.8% employed at baseline. Among the study participants, 68.4% were treatment-naïve, 19.2% had cirrhosis, 9.2% had history of anxiety, 15.8% history of depression, 11.5% of clinically overt fatigue, and 14.7% of type 2 diabetes. Demographic characteristics were generally balanced between the treatment groups (Table 1). The baseline PRO scores of patients from the two study arms are summarized in Supplementary Table 1 and were not different between the treatment groups (all p>0.02).

Treatment-related adverse events and the SVR rates are included in Table 1. More than half of treated patients did not experience any treatment-related adverse events during treatment, and the rates of all adverse events were similar between the active treatment arm and the placebo arm (all p>0.15). The SVR rate in the SOF/VEL arm was 99.0% (N=618/624), as reported previously [41]. Of the 6 patients who did not achieve SVR 12, there were 2 virologic failures and 4 patients who did not complete a post-treatment week 12 assessment.

Patient-reported outcomes during treatment with SOF/VEL
The dynamics in the summary PROs over time during and after treatment with SOF/VEL vs. placebo is shown in Figure 1. At each time point throughout post-treatment week 12, 84-88% of the intention-to-treat sample (both arms) had their PRO questionnaires completed; only the completed PRO items were used for calculations. Additionally, at post-treatment week 24, 78% of patients with SVR were followed-up.

The baseline PROs were similar between patients randomized to receive SOF/VEL and placebo (Supplementary Table 1). However, soon after treatment initiation, some PRO scores in the SOF/VEL arm began to increase indicating improvement of PRO scores. Indeed, by treatment week 4, statistically significant improvements were noted in GH (on average, +2.3 points on a 0-100 scale), EWB (+3.4), total FACIT-F (+1.3), all domains of CLDQ-HCV (+2.1 to +7.3) (all p<0.005). On the other hand, the only PRO which improved in patients who were receiving placebo was the worry domain of CLDQ-HCV: +4.6 (p=0.0016) while all other PROs either remained at baseline levels or moderately decreased (Supplementary Figure 1).

By treatment week 8, improvements in the same PROs of patients receiving SOF/VEL became more prominent (+2.8 in GH, +3.8 in EWB, +1.4 in total FACIT-F, up to +8.1 in CLDQ-HCV; all p<0.005). In contrast, the placebo arm again experienced either no change or decrements in their PROs except for the worry domain of CLDQ-HCV which was still higher when compared to the baseline level (+4.4) (p=0.005). The average change from baseline across 25 PROs in the placebo group was -2.6 vs. +1.1 in SOF/VEL (p<0.005 for RP, EWB, FACIT-F).
By the end of treatment week 12, the improvement in PRO scores with SOF/VEL continued with no improvement noted in the placebo group (Figure 2). It is also important to note that by treatment week 12, patients receiving placebo no longer experienced any improvement in their worry score (p>0.05), or any other PRO score.

Post-SVR patient-reported outcomes

Nearly all (618/624) patients who were treated with SOF/VEL achieved SVR, as opposed to zero in the placebo arm.

Four weeks after treatment cessation, the magnitudes of PRO improvement in subjects who received SOF/VEL became even greater in comparison to the end of treatment time point (on average across PROs, the improvement from baseline was +3.3, and p<0.005 for all but 5 PROs). In contrast, patients in the placebo arm remained at either their baseline levels or experienced moderate decline in their PRO scores: on average, -2.1, with the only improvement being observed again for the worry domain of CLDQ-HCV (+5.0, p=0.003). A similar trend was also reproduced at post-treatment week 12: +3.7 in patients with SVR-12 after SOF/VEL (all but 4 PROs had p<0.005) vs. -2.6 on average and no improvements in placebo patients (Supplementary Figure 2).

Finally, at post-treatment week 24, in patients who achieved SVR (77.6% of the initial active treatment group were followed-up at that time point), the average across PROs improvement was +5.4. (Figure 3).
**Independent predictors of PROs in ASTRAL-1**

Independent predictors of the summary PRO scores were assessed using longitudinal mixed models with adjustment for the baseline PRO levels and clinico-demographic PRO predictors. As a result of the time by regimen interaction term analysis, treatment-emergent changes in PROs were found to be independently predicted by receiving SOF/VEL as opposed to placebo both throughout treatment duration and in post-treatment follow-up. Indeed, the association of receiving SOF/VEL with greater PRO improvements was significant for FACIT-F and CLDQ-HCV while receiving treatment (beta=+3.6 and +2.5 points, respectively, p<0.005), and for all summary PROs after treatment discontinuation (beta=+3.6 to +4.9, all p<0.005) (Figure 4). Furthermore, in the placebo arm, there was no association of time with changes in PROs (all p>0.14), suggesting the no post-treatment improvements should be expected with this regimen. On the other hand, a similar association of completing SOF/VEL treatment (in comparison to being on-treatment) with PROs was found to be highly significant (beta range from +1.3 to +2.8, p<0.0001 for all summary PROs except for work productivity), thus, suggesting a consistently positive post-treatment dynamics in patient-reported outcomes.

**DISCUSSION**

This is the first study to report the impact of a pan-genotypic anti-HCV regimen (SOF/VEL) on patient-reported outcomes of patients with chronic hepatitis C. Our data indicate that the use of SOF/VEL leads to significant improvement in the majority of PRO domain scores measured with 4 different validated instruments during treatment and after achieving SVR. In fact, improvement of PRO scores started shortly after the initiation of therapy and continued to increase throughout treatment and after achieving SVR. It was interesting to note that after SVR-12, the magnitude of
PRO improvement continued, suggesting that additional PRO benefit could be found with longer follow-up.

In addition to providing evidence in support of the PRO benefit of SOF/VEL, this study makes another important contribution to the field of PRO assessment in HCV. One of the major criticisms and shortcomings of the previous PRO studies of all-oral regimens for HCV was the lack of placebo-controlled arms. In the absence of a placebo arm, there have been suspicions that the PRO improvements were related to the fact that patients who were being treated for their HCV were aware of their potential cure which may have potentially biased their PRO scores. The double-blind placebo-controlled study design of ASTRAL-1 provides a strong evidence that the improvement in PROs are real and are related to HCV viral suppression and not related to the “excitement” of receiving treatment.

Indeed, our data clearly demonstrated that the active regimen of SOF/VEL was the only arm of the study associated with PRO improvement. In contrast, patients who received an identical placebo in a blinded fashion did not experience improvement of their PRO scores. In fact, patients who initially experienced some improvement in their worry domain scores found that this improvement was short-lasting and did not persist throughout the treatment. We believe that this initial improvement in the worry domain in patients receiving placebo was due to their belief in getting treatment. However, due to the lack of viral suppression and the milieu of conditions associated with chronic hepatitis C, these factors continued to exert their detrimental effects affecting patients’ PRO burden.
In addition to reporting cross-sectional comparisons of PROs, to ensure that we were adjusting for any major contributors to PROs such as demographic and clinical factors, we also ran a series of multivariate analysis. These analyses indicated that the use of SOF/VEL was independently associated with moderate PRO improvement during treatment, while clearance of HCV infection was found to be strongly predictive of a significant improvement in PRO scores in post-treatment follow-up. In this context, our data provide additional evidence that the improvement of PROs during treatment and after achieving SVR is likely independent of the most expected confounders. The duration and consistent dynamics of post-SVR improvements in most of the studied PROs up to 24 weeks after treatment cessation also suggest that these improvements are sustainable in the long term rather than being a result of a temporary “euphoria” due to receiving an effective treatment regimen for HCV.

The underlying mechanisms to connect HCV clearance with PRO improvement are yet to be elucidated. Some putative mechanisms may be related to the improvement of cytokine profile due to the viral suppression which could in turn positively impact patients’ experience [46]. Another intriguing possibility is the impact of viral suppression on the brain metabolites since HCV has been detected in the subcortical white matter and brain stem [47]. Furthermore, it has been reported that viral clearance can lead to changes in some brain metabolites [47-48]. Thus, it is plausible that the early viral suppression may result in a reduction in cytokines and other substances in the periphery and the central nervous system leading to an improvement in “brain fog”, fatigue and other patient-reported outcomes related to HCV infection.
The study limitations primarily arise from the nature of any clinical trial study which has strict enrollment criteria and close follow-up. In this context, the findings from efficacy trials may potentially have limited generalizability to the entire HCV population. Additionally, some parameters which could potentially be associated with PROs were not collected during the study. These include level of education, marital status, income, type of work, etc. Finally, some of the PRO instruments were not systematically validated in all languages used in this study. Nevertheless, all these instruments have been systematically translated with some face and content validation [42-44, 49].

In summary, this placebo-controlled trial of SOF/VEL demonstrated significant and persistent improvement of PRO scores during treatment and after achieving SVR. Using these findings, we now have a comprehensive approach when treating and offering a possible cure to patients with chronic hepatitis C. We also emphasize that, when considering the effect of HCV treatment regimens, it is important to show not only efficacy and safety data but also the impact on patients’ experience using validated instruments for assessment of patient-reported outcomes.
REFERENCES


Table 1. Demographic characteristics and treatment-related adverse events in ASTRAL-1 patients.

<table>
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<tr>
<th></th>
<th>SOF/VEL</th>
<th>Placebo</th>
<th>p</th>
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<tbody>
<tr>
<td>N</td>
<td>624</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>54.05 ± 10.89</td>
<td>53.16 ± 10.35</td>
<td>0.41</td>
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<td>Male gender</td>
<td>374 (59.9%)</td>
<td>68 (58.6%)</td>
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<td>Caucasian</td>
<td>493 (79.0%)</td>
<td>89 (76.7%)</td>
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<tr>
<td>African-American</td>
<td>52 (8.3%)</td>
<td>12 (10.3%)</td>
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<td>Asian</td>
<td>62 (9.9%)</td>
<td>11 (9.5%)</td>
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<tr>
<td>Enrolled in the USA</td>
<td>234 (37.5%)</td>
<td>45 (38.8%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Employed at baseline</td>
<td>326 (63.2%)</td>
<td>71 (73.2%)</td>
<td>0.06</td>
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<td>Hemoglobin, g/dL</td>
<td>14.77 ± 1.31</td>
<td>14.86 ± 1.38</td>
<td>0.59</td>
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<tr>
<td>Treatment-naïve</td>
<td>423 (67.8%)</td>
<td>83 (71.6%)</td>
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</tr>
<tr>
<td>Cirrhosis</td>
<td>121 (19.5%)</td>
<td>21 (18.1%)</td>
<td>0.73</td>
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<tr>
<td>HCV genotype 1</td>
<td>328 (52.6%)</td>
<td>65 (56.0%)</td>
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<tr>
<td>HCV genotype 2</td>
<td>104 (16.7%)</td>
<td>21 (18.1%)</td>
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<td>HCV genotype 4</td>
<td>116 (18.6%)</td>
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<td>HCV genotype 5</td>
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<td>HCV genotype 6</td>
<td>41 (6.6%)</td>
<td>8 (6.9%)</td>
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<td>ALT &gt; 1.5 x ULN</td>
<td>279 (44.7%)</td>
<td>54 (46.6%)</td>
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<tr>
<td>HCV RNA &gt; 6 log 10/mL</td>
<td>440 (70.5%)</td>
<td>81 (69.8%)</td>
<td>0.88</td>
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<tr>
<td>History of:</td>
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<tr>
<td>Anxiety or panic disorders</td>
<td>58 (9.3%)</td>
<td>10 (8.6%)</td>
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<td>Depression</td>
<td>103 (16.5%)</td>
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<td>Clinically overt fatigue</td>
<td>72 (11.5%)</td>
<td>13 (11.2%)</td>
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<tr>
<td>Sleep disorders</td>
<td>96 (15.4%)</td>
<td>13 (11.2%)</td>
<td>0.24</td>
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<td>Type 2 diabetes or hyperglycemia</td>
<td>64 (10.3%)</td>
<td>14 (12.1%)</td>
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<td>Body mass index</td>
<td>26.67 ± 5.04</td>
<td>25.92 ± 4.24</td>
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<td>Treatment-related adverse events:</td>
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<td>Blood-related or anemia</td>
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<td>Fatigue or asthenia</td>
<td>124 (19.9%)</td>
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<td>No adverse events</td>
<td>318 (51.0%)</td>
<td>64 (55.2%)</td>
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<td>Sustained virologic response</td>
<td>618 (99.0%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.0001</td>
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Figure legends

**Figure 1.** Summary PROs in patients with HCV treated with SOF/VEL and placebo. The FACIT-F PROs (chart B) were transformed to the uniform 0-100 scale. Abbreviations: PCS – physical component summary of SF-36; MCS – mental component summary of SF-36; FS – fatigue scales of FACIT-F; FACIT-F – the total FACIT-F score; AE – activity/energy score of CLDQ-HCV; CLDQ-HCV – the total CLDQ-HCV score; WI – work productivity impairment of WPAI:SHP; AI – activity impairment of WPAI:SHP.

**Figure 2.** Treatment-emergent changes in PROs in patients after receiving SOF/VEL and placebo for 12 weeks. A grey asterisk indicates statistically significant difference between the study arms (p<0.005); a red asterisk indicates statistically significant change from the baseline level (difference from zero). All PROs were transformed to a uniform 0-100 scale. A zero height bar indicates no change from the baseline level.

**Figure 3.** Post-treatment week 24 follow-up changes in PROs in patients who achieved SVR after receiving 12 weeks of SOF/VEL (78.3% of all patients with SVR). A zero height bar indicates no change from the baseline level. All PROs were transformed to a uniform 0-100 scale. The changes above the red line are statistically significant with reference to the baseline levels (p<0.005).

**Figure 4.** Independent association with summary PROs in a mixed longitudinal model of the use of SOF/VEL (the reference treatment: placebo) (A) while receiving treatment, and (B) after