**Point-By-Point Response**

1. *Evaluation and comparing different regimens of DDAs therapy, specially SOF, in real world for CHC has been addressed in several new reports. Results of these new reports should be carefully compared and discussed in the present manuscript. In fact, the manuscript needs a careful updating based on new reports specially those appeared in 2017 (which are currently absent in the present manuscript). Some examples are in the following: - Dual treatment with sofosbuvir plus ribavirin is as effective as triple therapy with pegylated interferon plus sofosbuvir plus ribavirin in predominant genotype 3 patients with chronic hepatitis C. Satsangi S, Mehta M, Duseja A, Taneja S, Dhiman RK, Chawla Y. J Gastroenterol Hepatol. 2017 Apr;32(4):859-863. doi: 10.1111/jgh.13595. - Sofosbuvir-based treatment regimens: real life results of 14 409 chronic HCV genotype 4 patients in Egypt. Elsharkawy A, Fouad R, El Akel W, El Raziky M, Hassany M, Shiha G, Said M, Motawea I, El Demerdash T, Seif S, Gaballah A, El Shazly Y, Makhlouf MA, Waked I, Abdelaziz AO, Yosry A, El Serafy M, Thursz M, Doss W, Esmat G. Aliment Pharmacol Ther. 2017 Mar;45(5):681-687. doi: 10.1111/apt.13923. Epub 2017 Jan 9. - Early Experience of Sofosbuvir based Combination Therapy in "Real-Life" Cohort with Chronic Hepatitis-C Infection. Mehta R, Kabrawala M, Nandwani S, Tekriwal R, Nandania P. J Clin Diagn Res. 2017 Mar;11(3):OC05-OC08. doi: 10.7860/JCDR/2017/23184.9335. Epub 2017 Mar 1. - Combination of sofosbuvir, pegylated-interferon and ribavirin for treatment of hepatitis C virus genotype 1 infection: a systematic review and meta-analysis. Dolatimehr F, Karimi-Sari H, Rezaee-Zavareh MS, Alavian SM, Behnava B, Gholami-Fesharaki M, Sharafi H. Daru. 2017 Apr 20;25(1):11. doi: 10.1186/s40199-017-0177-x. - Curing Chronic Hepatitis C: A Cost Comparison of the Combination Simeprevir Plus Sofosbuvir vs. Protease-Inhibitor-Based Triple Therapy. Langness JA, Tabano D, Wieland A, Tise S, Pratt L, Harrington LA, Lin S, Ghuschcyan V, Nair KV, Everson GT. Ann Hepatol. 2017 May - Jun;16(3):366-374. doi: 10.5604/16652681.1235479. - A pangenotypic, single tablet regimen of sofosbuvir/velpatasvir for the treatment of chronic hepatitis C infection. Weisberg IS, Jacobson IM. Expert Opin Pharmacother. 2017 Apr;18(5):535-543. doi: 10.1080/14656566.2017.1282459. Epub 2017 Mar 24. Review.*

   We agree that some more recent references that were not included in the original submission should have been, and greatly appreciate the reviewer's suggestions. We have included the suggested references, and discuss the data included in these studies. In the final paragraph of the Introduction section (page 7, paragraph 2) we have modified the last paragraph to read:

   > "We previously established that the cost-per-SVR of TVR-based triple therapy in clinical practice approached $200,000—far higher than projections based on results of randomized clinical trials [19]. In the present study, we examine the clinical and economic performance of regimens containing SMV and/or SOF in a consecutive series of 508 patients and identify risk factors associated with treatment success (SVR12) or failure. SMV remains an important option for patients with resistance associated variants (RAVs) to NS5A inhibitors, and in liver transplantation recipients

[21–23]. Prior studies assessing outcomes of SMV- and/or SOF-containing regimens in clinical practice were limited to patients with GT 1 HCV **[24–28]. Other recent studies assessing real-world outcomes of SOF-based dual- or triple-therapy have focused on patients with a single genotype.** **[29,30]** Here we offer a comprehensive examination of real-world outcomes of three different treatment regimens across genotypes 1-4."

Further, we have modified several parts of the **Discussion** section to reflect our inclusion of this newer data. On page 14, paragraph 3 and page 15, paragraph 2 and 3, we comment:

"Whereas real-world SVR12 rates with TVR- and BOC-containing regimens were lower than in large registration trials [18,37], the SVR12 rates in this study generally accord with results obtained in formal trials. Among the 508 patients who began therapy, SVR12 rates calculated on an ITT basis were 86% for SMV/SOF ± RBV, 62% for SOF/RBV, and 78% for SOF/PEG/RBV. For comparison, in registration trials, SVR12 rates for SMV/SOF ± RBV ranged from 83%-97% [7,8]; for SOF/RBV, they ranged from 56-97% [6]; and for SOF/PEG/RBV, they ranged from 80-90% [6]. The relatively low overall SVR12 rate for SOF/RBV in our population likely reflects the fact that 48% (113/234) of patients treated with SOF/RBV had GT 1 or GT 4 HCV. Published data show that SVR12 rates may be lower for these genotypes, especially in the setting of advanced liver disease [32]. **Patients with GT 3 HCV also had a relatively lower rate of SVR12 at 67%; this is similar to the SVR12 rate seen in another recent study assessing real-world rates of SVR12 in patients with GT3 HCV, where the SVR12 rate was 69.4%** [38]. In contrast, patients in our study with GT 2 HCV who were treated with SOF/RBV had an SVR12 rate of 83% (95% CI: 71-90%), again consistent with the high rate of response to SOF/RBV for GT 2 as published in the literature. Among patients treated with either SMV/SOF ± RBV or SOF/PEG/RBV, GT did not impact significantly upon SVR12 rates.

Multivariable logistic regression identified factors associated with lower SVR12 rates, helping to define patients who may benefit from alternative treatment strategies. Among all treatment regimens examined, the presence of more advanced liver disease was negatively associated with achieving an SVR12. **These findings accord with another recently published study assessing treatment outcomes among patients with GT4 HCV treated with SOF/RBV or SOF/PEG/RBV, where those with advanced liver disease were less likely to achieve SVR12.[30]** The observation that more advanced liver disease was associated with treatment failure across all three regimens is noteworthy because advanced liver disease is becoming increasingly prevalent in patients with HCV infection [38,39]. This underscores the urgency of efforts to screen patients for HCV infection and transition them into care in order to minimize liver disease progression.

Cost of HCV eradication has become a major concern for the general public and the

medical community [40]. We previously analyzed costs of TVR-based triple therapy and found that TVR, which at the time cost $4,606/week, accounted for the majority of the expenses [19]. The costs of both SMV ($5,530/week) and SOF ($7,000/week) are higher than TVR. **In part because of this increased drug cost, data from a recently published study suggested that cost-per-SVR was relatively constant when comparing SMV/SOF ± RBV with TVR-based triple therapy [27]. In contrast, our data suggest that the median cost-per-SVR for SMV/SOF ± RBV is significantly lower than that of TVR-based treatment, likely because of a shorter duration of treatment, reduced adverse event management costs, and higher SVR12 rates compared with TVR-based regimens. Heterogeneity in the demographic makeup and percentage of patients with advanced fibrosis/cirrhosis in study populations may account for the discordant results."**

Finally, we comment on the newer data surrounding sofosbuvir/velpatasvir in the 3rd paragraph on page 16:

"While DAAs remain expensive, it is hoped that the increasing number of treatment options and increased competition will drive costs down. This may especially be important in emerging economies [41]. In addition to occupying a place in the global market, SMV will likely play an important role in specific settings, including the treatment of HCV after liver transplantation, where it has been used successfully without RBV with SVR12 rates ranging from 78-88% [23,25,42,43]. SMV may also play an important role in patients with a history of failed NS5A inhibitor therapy. Approximately 5-15% of patients may fail therapy with regimens containing NS5A inhibitors such as ledipasvir, elbasvir, or daclatasvir. These treatment failures often occur in patients with RAVs of HCV, some of which may confer cross-resistance for multiple drugs within this class [44]. In patients who fail NS5A therapy, treatment with SMV/SOF can result in an SVR12 rate of 88% [21]. RAV testing is becoming more common, as it is recommended by AASLD guidelines prior to initiation of therapy with elbasvir/grazoprevir [45]. **While the newest NS5A inhibitor, velpatasvir (used in fixed-dose combination with SOF) may be impacted less by the presence of pretreatment RAVs, this regimen remains expensive and may not be accessible to all patients [46].** More precise targeting of therapy may improve patient outcomes and reduce costs."

2. *Please define SVR12 in abstract and explain the difference between SVR and SVR12.*

The abstract has been updated to more explicitly define SVR12, and now reads:

"…patients with genotypes 1 through 4 were included. **Rates of sustained virological response – the absence of a detectable serum HCV RNA 12 weeks after the end of treatment (SVR12)** – were calculated on an intention-to-treat basis."

The difference between SVR and SVR12/24 has been fleshed out in the text, where paragraph 1 in the **Introduction** section reads:

> "**...SVR is equivalent to a virological cure, and is currently defined as the absence of detectable HCV RNA in blood 12 weeks after the end-of-treatment (EOT). SVR at 12 weeks (SVR12) has supplanted SVR at 24 weeks as the standard endpoint [11].**"

3. *Authors emphasis (even in the abstract) that the involved patients were infected with HCV genotypes 1 to 4 but no result/discussion based on genotype and SVR is provided. Please reconsider.*

We agree that the discussion surrounding the impact of genotype on SVR rates required further detail. To address this, we have added additional details within the result section and in the discussion. In the first paragraph of the **Results** section (page 10, paragraph 3) we have added:

> **"Of patents treated with SMV/SOF ± RBV, 99% were GT 1, compared with 87% of patients treated with PEG/RBV/SOF and 44% treated with SOF/RBV. The remaining distribution of HCV GTs in each treatment group is displayed in Table 1."**

In the **Results** section under the subheading **Real-World SVR12 Rates** (page 11, paragraph 2), we have added:

> "The overall SVR12 rate was 73% (95% CI: 69%-77%). It was 86% (95% CI: 80%-91%) among patients on SMV/SOF ± RBV, 62% (95% CI: 55%-68%) among patients on SOF/RBV, and 78% (95% CI: 68%-86%) among patients on SOF/PEG/RBV. Among patients treated with SMV/SOF ± RBV in the "COSMOS-like" cohort (which excluded patients who had previously failed a PI and/or had Child-Pugh class B or C cirrhosis), the SVR12 rate was 90% (95% CI: 83-94%). This is similar to the SVR12 rate in the COSMOS study, which was 92% for patients with METAVIR scores F0-2 and 94% for patients with METAVIR scores F3-4 [33]. **SVR12 rates varied by GT for patients treated with SOF/RBV, and ranged from 44% (95%CI: 34-54%) for GT 1 to 83% (95%CI: 71-90%) for GT 2 (Table 3). A comparison between SVR12 rates with regards to GT was not statistically feasible in the group receiving SMV/SOF ± RBV as only one patient in this group was infected with GT 4. SVR12 rates did not differ significantly between patients with GT 1 and GT 4 HCV in the group treated with SOF/PEG/RBV.**"

In paragraph 3 of the **Discussion** section (page 14, paragraph 3), we discuss the impact that genotype had on SVR12 for each regimen. Notably, all but one patient treated with SMV/SOF

+/- RBV was genotype 1, limiting analysis by genotype in that group. Among patients treated with SOF/PEG/RBV, genotype did not impact significantly upon SVR12.

> "Whereas real-world SVR12 rates with TVR- and BOC-containing regimens were lower than in large registration trials [18,37], the SVR12 rates in this study generally accord with results obtained in formal trials. Among the 508 patients who began therapy, SVR12 rates calculated on an ITT basis were 86% for SMV/SOF ± RBV, 62% for SOF/RBV, and 78% for SOF/PEG/RBV. For comparison, in registration trials, SVR12 rates for SMV/SOF ± RBV ranged from 83%-97% [7,8]; for SOF/RBV, they ranged from 56-97% [6]; and for SOF/PEG/RBV, they ranged from 80-90% [6]. **The relatively low overall SVR12 rate for SOF/RBV in our population likely reflects the fact that 48% (113/234) of patients treated with SOF/RBV had GT 1 or GT 4 HCV. Published data show that SVR12 rates may be lower for these genotypes, especially in the setting of advanced liver disease [32]. Patients with GT 3 HCV also had a relatively lower rate of SVR12 at 67%; this is similar to the SVR12 rate seen in another recent study assessing real-world rates of SVR12 in patients with GT3 HCV, where the SVR12 rate was 69.4% [38]. In contrast, patients in our study with GT 2 HCV who were treated with SOF/RBV had an SVR12 rate of 83% (95% CI: 71-90%), again consistent with the high rate of response to SOF/RBV for GT 2 as published in the literature. Among patients treated with either SMV/SOF ± RBV or SOF/PEG/RBV, GT did not impact significantly upon SVR12 rates."**