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ORIGINAL ARTICLE

Open-Label Study to Evaluate the Safety & Tolerability of Telaprevir in Combination With Sofosbuvir in Naive Subjects Infected With Hepatitis C Virus Genotype 1

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ABSTRACT

AIMS: Sofosbuvir is a potent hepatitis C Virus (HCV) NS5B RNA polymerase inhibitor that has led to high-sustained viral response rates when combined with other direct-acting antivirals. To date, no data exists on the combination of sofosbuvir with the NS3 protease inhibitor, telaprevir. The safety, tolerability, and efficacy of an all-oral 12-week regimen of telaprevir in combination with sofosbuvir were evaluated in this open-label, phase 2 study.

METHODS: Twenty adults with HCV genotype 1 infection who were non-cirrhotic and naïve to therapy received telaprevir 1125 mg orally twice-daily plus sofosbuvir 400 mg once daily for 12 weeks.

RESULTS: Telaprevir plus sofosbuvir was generally well tolerated, with all 20 subjects completing treatment. The five most common adverse events were nausea, rash, headache, ano-rectal symptoms, and pruritus. Two subjects required discontinuation of telaprevir after week 4 but were maintained on sofosbuvir till the end of treatment. Sustained virologic response 12 weeks after the end of treatment was 95%.

CONCLUSION: The results provide valuable information regarding the safety, tolerability and efficacy of telaprevir combined with sofosbuvir as dual therapy in naïve non- cirrhotic HCV genotype 1 infected patients.

Key words: Antiviral agent; Clinical trial; Combination drug therapy; Protease inhibitor; Nucleotide polymerase inhibitor

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Abbreviations

HCV: hepatitis C; SVR: sustained viral response; AE: adverse event; TVR: telaprevir; SOF: sofosbuvir; EOT: end of treatment; DSMB: data safety monitoring board; IL28B: interleukin-28B; PK: pharmacokinetics.

INTRODUCTION

It has been estimated that between 2% - 3% of the global population,

is infected with Hepatitis C virus (HCV) corresponding to approximately 130-170 million individuals[1-4]. In the United States, chronic hepatitis C virus is the most common cause of liver disease and can lead to cirrhosis, liver failure, and hepatocellular carcinoma. HCV is responsible for greater than 15,000 deaths annually in the United States and the morbidity and mortality associated with HCV infection will continue to increase over the next few decades[5-7]. The 2011 approval of two HCV protease inhibitors, boceprevir and telaprevir represented the first introduction of direct acting antivirals (DAAs) DAAs into the management of chronic hepatitis C and dramatically improved cure rates for patients who could tolerate an interferon-based regimen[8-12].

Despite the advantages of higher sustained viral response (SVR) with telaprevir and boceprevir, issues of viral resistance and increased adverse effects (AEs) require close medical management and appropriate patient selection. These interferon containing therapies remain unpleasant to administer and are associated with significant side effects resulting in high rates of non-compliance and apprehension about starting treatment. Thus, many patients have preferred continued to avoid interferon-based therapy, highlighting the need for new regimens that are more effective (especially in patients infected by genotype 1), better tolerated and easier to administer.

Telaprevir (TVR) has been explored in all-oral combinations. In a phase 2 study (ZENITH) the safety, tolerability, and antiviral activity of VX-222, a selective, non-nucleoside inhibitor of HCV NS5B polymerase, in combination with TVR (with and without ribavirin) in genotype 1 HCV infection was studied[13]. Despite the discontinuation of the combination regimen due to high viral breakthrough rates prior to week 12 the study provided valuable information regarding the safety, tolerability, and efficacy of TVR in DAA combinations without interferon. Telaprevir, with or without ribavirin, was generally well tolerated[13].

Sofosbuvir (SOF) is a first in class nucleotide analog chain terminator that has performed extremely well in oral combinations. In combination with daclatasvir, an HCV NS5A replication complex inhibitor, SVR rates for genotype 1 treatment-naïve and treatment experienced patients plus or minus the addition of ribavirin ranged from 95 to 100% and was well tolerated[14]. Results from the Phase 3 studies of sofosbuvir in combination with peginterferon alfa 2a and ribavirin and with ribavirin alone led to the initial FDA approval of sofosbuvir in combination with peg-interferon and ribavirin (for genotype 1) and as a single agent combined only with ribavirin (for genotype 2 and 3)[15]. Excellent SVR rates and patient tolerability were seen when SOF was combined with simeprevir, a NS3/4A HCV protease inhibitor. 16 In fact, this combination therapy has been embraced as a preferred therapy for select genotype 1 populations and was granted FDA approval for treatment-naïve or treatment experienced cirrhotic and non-cirrhotic patients[16,17]. The results from the combination of SOF with a protease inhibitor supports the rationale for the co-administration of TVR and SOF

This study was performed to evaluate the safety, efficacy, and potential drug-drug interactions and development of drug resistance of the combination of TVR and SOF, a potent HCV protease inhibitor and a potent HCV nucleotide inhibitor, respectively.

METHODS

Patients

Eligible for inclusion were subjects aged 18 years and older who were treatment-naïve, had genotype 1 HCV infection, plasma HCV RNA levels of at least 1,000 IU/mL, BMI greater than 18 kg/m^2, and females/males practicing acceptable forms of contraception. Subjects demonstrating evidence of cirrhosis by liver biopsy, APRI/FibroSureTM, and or Fibroscan (>10 kPa) were excluded from the study. Other key exclusion criteria included seropositivity for hepatitis B serum antigen or HIV type 1 or 2; other liver diseases; creatinine clearance less than 60 mL/min.

Study design

STEADFAST was a phase 2, open label pilot study conducted at two sites in the USA (clinicaltrials.gov identifier: NCT01994486). The study evaluated the safety and tolerability, and antiviral efficacy of TVR in combination with SOF for 12 weeks in treatment naïve subjects with genotype 1, chronic HCV infection. TVR was administered orally at a dosage of 1125 mg twice daily with food. SOF was administered orally at a dosage of 400 mg daily with the morning dose of TVR.

The plan was to enroll 20-treatment naïve subjects and collect evaluable safety and SOF PK data. An evaluable subject was defined as any subject with at least 4 weeks of therapy duration. Treated subjects who discontinued for any reason prior to 4 weeks were to be replaced.

After clearing the screening process, subjects presented for on-treatment assessment at baseline, day 3, weeks 1, 2, 3, 4, 6, 8, 10 and 12.

Follow-ups (FU) visits were conducted to monitor safety and virologic outcomes at post-treatment week 4. Virologic outcomes were monitored at post-treatment Weeks 4, 12 and 24. All subjects who terminated treatment early for virologic failure completed the End of Treatment (EOT) visit and all post-treatment FU visits (FU week 4, FU week 12) for viral NS3/4A and NS5B domains amino acid (a a) sequencing. The following criteria were used to define discontinuation as a result of virologic failure; Confirmed HCV RNA greater than lower limits of quantification (LLOQ); Confirmed > 1 log10 increase from lowest level (nadir). If the retest was lower than 500 IU/mL, it needed to be more than the first viral RNA measurement ⩾25 IU/mL; Confirmation of viral RNA was performed within 2 weeks after the initial observation indicating virologic failure during the on-treatment phase.

All subjects who terminated treatment early for virologic failure completed the EOT visit and all post-treatment FU visits (FU4, FU12) in order to sequence the HCV NS3•4A protease domain and the HCV NS5B domain.

Discontinuations of study medications for reasons other than virologic breakthrough were performed if the subject experienced a laboratory or clinical event. There was no option for dose reduction of TVR or SOF. TVR could be permanently discontinued due to laboratory abnormality or clinical adverse event without stopping SOF (SOF monotherapy) if the patient had received at least 4 weeks of combined dosing. If TVR dosing had been discontinued, it could not be restarted. There were no options for TVR monotherapy dosing.

The study had an independent Data Monitoring Committee (DMC) that evaluated the study after 60% of enrolled patients completed 28 days of therapy. The institutional review board at each site approved the study protocol. All patients provided written informed consent. This study was conducted in accordance with the Good Clinical Practice Guidelines of the International Conference of Harmonization, the principles of the Declaration of Helsinki, and local regulations.

Assessments

The primary assessment was the safety and tolerability of TVR and SOF when dosed in combination for 12 weeks. Treatment-emergent adverse events (AEs) and serous AEs were monitored to assess tolerability. Physical examinations, vital signs, ECGs, and laboratory assessments were monitored to assess safety. Skin rash reactions were graded as mild, moderate, severe, or potentially life threatening.

Secondary assessments included the proportion of subjects who achieved undetectable HCV RNA 4 weeks (SVR 4) after the last dose of the assigned study drug treatment; the proportion of subjects who achieved undetectable RNA 12 weeks (SVR 12) after the last dose of the assigned study drug treatment; proportion of subjects who achieve undetectable RNA levels at weeks 1,2,4 and end of treatment; proportion of subjects who a viral breakthrough; time to virologic breakthrough; proportion of subjects who have a viral relapse; amino acid (aa) sequence of the HCV NS5B polymerase domain and aa sequence of the HCV NS3/4A protease domain in patients with a treatment failure (breakthrough or relapse). Plasma HCV RNA levels were assessed using the COBAS® TaqMan® HCV RNA assay test (v2.0; Roche Diagnostics, Indianapolis, IN, USA; LLOQ=25 IU/ml; limit of detection=15 IU/mL). Values <LLOQ were reported as "<25IU/mL, HCV RNA not detected" or as 'HCV RNA detected.' HCV RNA assessments were performed at baseline, day 3, week 1, 2,3,4,6,8,10,12,16, and 24. Amino acid changes from baseline sequence in the HCV NS5B and NS3/4A domains were determined by population sequencing to identify potential resistance mutations associated with TVR and/or SOF. This was performed in patients who stopped treatment because of viral breakthrough, completed or prematurely discontinued treatment, but had detectable HCV RNA levels at end of study.

Experimental assessments included genotyping for interleukin-28B (IL28B) subtypes (CC, CT, and TT). Blood samples were collected for DNA analyses on day 1, before dosing. Evaluation of IL28B genotype at rs12979860 was performed using a validated real-time, quantitative PCR assay designed to distinguish CC, CT, and TT subtypes in DNA isolated from whole blood. As previously described, HCV genotype and subtype were determined at baseline using VERSANT genotype 2.0 assay (INNO-LiPA;Innogenetics, Ghent Belgium).

Statistical analysis

Assessment of safety was the primary consideration in choosing the sample size, *n*= 20 subjects. This sample size provided a high probability (87.8%) of observing an adverse event in at least 1 subject when the underlying incidence rate is 10% or greater.

The key efficacy assessment was the proportion of subjects who achieved SVR12. An exact 95% CI calculated under the assumption that observed SVR12 may vary between 70 and 80% suggested that a sample size of 20 subjects provided a reasonable precision to determine SVR12 rates.

Efficacy analyses were based upon on all patients who received at least one dose of the study drugs.

All patients participated in a sparse pre-dose PK sampling at week 2 and week 10. Eight subjects consented to participate in an intensive PK sub-study at week 2. The intensive serial PK sub-study performed at week 2 obtained samples over a 6-hour post-dose period measuring the steady-state pharmacokinetics of SOF and its metabolites.

RESULTS

Twenty subjects were enrolled in STEADFAST. Table 1 shows baseline demographics and disease characteristic for the study population. Subjects were predominately Caucasian (95%), female (65%), with a mean age of 51 years, mean BMI of 27. At baseline mean HCV RNA was 6.0×10^6 copy/mL, 85% had genotype 1a HCV, and mean Aspartate transaminase to platelet ratio index (APRI) score of 0.64. All twenty subjects completed

12 weeks of the scheduled treatment. Of the twenty subjects, no subjects met virologic stopping rule by week 4 of treatment. Two subjects (10%) discontinued TVR after week 4 due to intolerance but continued on SOF alone until the end of treatment.

Table 1 Patient baseline demographics.

Characteristic	TVR + SOF (n = 20)
Mean age (range) (years)	51 (20-79)
BMI [mean (range)] (kg/m^2)	27 (24-33)
Sex	
Male [n (%)]	7 (35%)
Female [n (%)]	13 (65%)
Race [n (%)]	
Caucasian	19 (95%)
African American	1 (5%)
HCV genotype 1 subtype [n (%)]	
1a	17 (85%)
1b	3 (15%)
IL28B genotype [n (%)]	
CC	10 (50%)
CT	7 (35%)
TT	3 (15%)
Baseline HCV RNA levels (IU/mL) Log10 (mean ST±log10≥log10 (mean STNA	5,975,504.5
APRI score	0.64 (0.11- 3.18)

Safety and tolerability

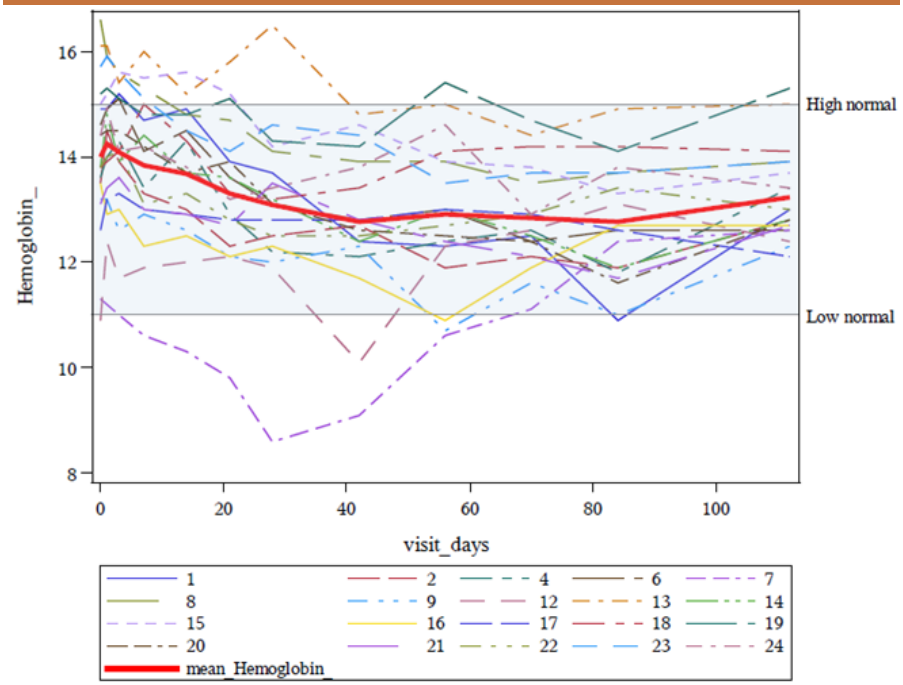
A total of 103 adverse events (AEs) occurred during the study. The most common AEs as noted in table 2 during the 12 weeks of treatment were nausea (45%), rash (40%), headache (30%), ano-rectal symptoms (30%), Pruritus (25%) fatigue (20%), and constipation (20%). The mean Hgb drop at week 12 was 1.50 g/dL; and there was only one incident of moderate anemia (grade 3) observed in the study treatment period (Table 3). One patient experienced moderate pruritis (grade 2) and another had anemia (grade 3). Both of these adverse events required the discontinuation of TVR after week 4 of study treatment. In addition there was one serious adverse event (SAE) of bradycardia that occurred following a subject's (non-prescribed) use of a potassium supplement. Both the investigators and the DSMB reported that this SAE was not related to the study medications, and was likely caused by hypokalemia from potassium supplement.

Table 2 Adverse events during the study treatment period.

Adverse Events[1]	DAIDS Gr 1	DAIDS Gr 2	DAIDS Gr 3	DAIDS Gr 4	Total [n (%)]
Nausea	8	1	0	0	9 (45%)
Rash	6	2	0	0	8 (40%)
Headache	5	1	0	0	6 (30%)
Anorectal Sx's	4	2	0	0	6 (30%)
Pruritus	4	1	0	0	5 (25%)
Constipation	3	1	0	0	4 (20%)
Fatigue	0	4	0	0	4 (20%)
Bradycardia[2]	0	0	0	1	1 (5%)

[1]Most common AEs were defined as those events occurring greater than 20% of the time; [2] SAE – Bradycardia, Cardiac Arrhythmia: outcome resolved. Unrelated to SOF-TVR combination per investigator and DSMB.

Table 3 Hemoglobin values plots by patient.



THE BOLD RED LINE represents the mean Hgb level throughout. The mean hemoglobin drop at week 12 was 1.5 g/dL. One subject was maintained on SOF monotherapy due to hemoglobin decline.

Virologic Response

Subjects receiving the combination of TVR and SOF achieved an initial rapid decline in HCV RNA levels; 18/20 (90%) achieved <LLOQ undetectable HCV RNA at week 2, and 20/20 (100%) achieved <LLOQ undetectable HCV RNA at week 4 (rapid virologic response) (Table 4). One subject reported non-compliance with regimen and had a viral breakthrough between weeks 10 and 12 of treatment. Non compliance in this subject was confirmed by PK assessment. SVR12 and SVR24 was achieved in 19/20 (95%) subjects.

Viral Sequencing

NS5B and NS3/4A population sequencing was performed on all baseline samples. With the exception of one patient for whom the NS5B assay failed, all baseline samples were successfully sequenced. A few of the Day 3 samples with lower viral loads (<~1000 IU/mL) failed as well. Of the baseline and Day 3 samples sequenced, all were wild-type (NCBI reference ID AF009606 for genotype 1a and AJ39799 for genotype 1b) with the exception of one patient who had an NS3 IIe132Val polymorphism. This IIe132Val variant is most often seen in combination with other resistant associated mutations, but by itself is not resistant to TVR. No NS3/4A or NS5B variants present at baseline were associated with treatment failure. The single patient who experienced viral breakthrough had no known resistance mutations detected (eg; wild-type), which is consistent with reason for failure being non-compliance.

PK Analysis

Mean sofosbuvir, GS-331007, and GS-566500 predose trough plasma concentrations showed that all three compounds had comparable concentrations after 2-weeks and 10-weeks of dosing indicating that steady-state was achieved after 2 weeks of dosing. Of note, the PK analysis appropriately identified undetectable levels of sofosbuvir and its metabolites at Week 10 in the noncompliant subject

Following co-administration of sofosbuvir and telaprevir for 2-weeks in the eight patients participating in the Intensive PK sub study, the pharmacokinetic parameters of sofosbuvir and its metabolite are presented in table 5.

In previous studies with sofosbuvir (alone or with Pegylated interferon and ribavirin) in HCV subjects, the steady state AUC_{0-} of sofosbuvir and GS-331007 was reported to be 969 and 6,790 ng·h/mL, respectively[18]. Therefore, upon co-administration with telaprevir, the exposure of the prodrug, sofosbuvir, was increased about 2.5-fold, while the exposure of its major metabolite, GS-331007 was decreased by about 31%. The steady-state AUC0-□ of GS-566500 has been previously reported to be about 1,315 ng·h/m[19]. Therefore, upon co-administration with telaprevir, the exposure of GS-566500 was increased about 4.3-fold.

Table 4 Key Virologic Assessment.

Assessment [*n* (%)]	TVR + SOF (*n* = 20)
12 week treatment period: weeks 1-12	
< LLOQ undetectable HCV RNA [n (%)]	
Week 1	8 (40%)
Week 2	18 (90%)
Week 4 (Rapid Virologic Response)	20 (100%)
Week 8	20 (100%)
Week 12	19 (95%)
Sustained virologic response	
SVR12	19 (95%)
SVR 24	19 (95%)

Table 5 Steady-state pharmacokinetic parameters of sofosbuvir and its major metabolites after two weeks of co-administration with telaprevir [Mean (SD)].

	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)
Sofosbuvir	2475 (1056)	3850 (1026)
GS-331007	976 (228)	4672 (824)
GS-566500	1498 (577)	5689 (2073)

DISCUSSION

This study evaluated the combination of telaprevir with sofosbuvir in genotype 1, treatment-naïve patients infected with HCV genotype 1 naïve HCV-infected patients. Overall the combination of TVR+SOF was well tolerated with the most common AEs by system organ class were those related to gastrointestinal (nausea), and skin (rash, pruritus) that have been previously associated with telaprevir use[8]. Rapid virologic response was observed with this combination of TVR+SOF. With exception of the one non-compliant subject whose noncompliance was confirmed in the intensive PK sub study analysis and no detected resistance, sustained viral response was achieved in 95% of participating patients.

The increase in sofosbuvir exposure with telaprevir is not expected to be clinically important as it is similar to the effect of cyclosporine on sofosbuvir which does not merit a change in the dosage of sofosbuvir[19]. The clinical significance of the increased levels of the sofosbuvir metabolite, GS-566500, during the co-administration of telaprevir is not known.

Despite the fact the telaprevir is no longer available in the US market, it remains in clinical use in much of the world. The results of this small study provide clinicians with preliminary safety and efficacy data on the combination of telaprevir and sofosbuvir.

CONCLUSION

Valuable information regarding the safety, tolerability, and efficacy of telaprevir in combination with sofosbuvir was obtained in this pilot study. The results demonstrate that the combined regimen of telaprevir and sofosbuvir led to a rapid antiviral response and showed SVR rates comparable to other DAA combinations previously studied[16,17,20]. The clinical significance of the increased levels of the sofosbuvir metabolite, GS-566500, during the co-administration of telaprevir is not known.

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CONFLICT OF INTERESTS

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REFERENCES

1 Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin Liver Dis*; 14:1-21, vii.
2 Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007;13:2436-41
3 Alter MJ1, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999;341:556-62
4 Rustgi VK. The epidemiology of hepatitis C infection in the United States. *J Gastroenterol* 2007;42:513-21
5 Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. *Dig Liver Dis*. 2011;43:66-72
6 Cohen J. The scientific challenge of hepatitis C. *Science* 1999; **285**: 26-30
7 Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; **138**: 513-21, 21 e1-6.
8 Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med.* 2011 Jun 23; **364(25)**: 2405-2416
9 Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP; SPRINT-2 Investigators. SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-206
10 McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, Heathcote EJ, Zeuzem S, Reesink HW, Garg J, Bsharat M, George S, Kauffman RS, Adda N, Di Bisceglie AM; PROVE3 Study Team. PROVE3 Study Team. Telaprevir for previously treated chronic HCV infection. *N Engl J Med*. 2010 Apr 8; **362(14)**: 1292-1303
11. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R; HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; **364**: 1207-1217
12 Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M; REALIZE Study Team. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011 Jun 23; **364(25)**: 2417-2428

13 Di Bisceglie AM, Sulkowski M, Gane E, Jacobson IM, Nelson D, DeSouza C, Alves K, George S, Kieffer T, Zhang EZ, Kauffman R, Asmal M, Koziel MJ. VX-222, a non nucleoside NS5B polymerase inhibitor, in telaprevir-based regimens for genotype 1 hepatitis C virus infection. *Eur J Gastroenterol Hepatol* 2014 Jul; **26(7)**: 761-73

14 Sulkowski MS, Gardiner DF, Rodriguez-Torres M. High rate of sustained virologic response with the all-oral combination of daclatasvir (NS5A Inhibitor) plus sofosbuvir (nucleotide NS5B inhibitor), with or without ribavirin, in treatment-naive patients chronically infected with HCV genotype 1, 2, or 3 (Abstract LB-2). Paper presented at: 63rd Annual Meeting of the American Association for the Study of Liver Diseases; 2012 November 9–13; Boston, MA.

15 Yamada I1, Suzuki F, Kamiya N, Aoki K, Sakurai Y, Kano M, Matsui H, Kumada H. Safety, pharmacokinetics and resistant variants of telaprevir alone for 12 weeks in hepatitis C virus genotype 1b infection. *J Vir Hepatol* 2012; 19:e112-e119.

16 Jacobson IM, Ghalib, R, Rodriguez-Torres, M, Younossi, M. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. Presented at 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in Washington, DC. Monday, November 4, 2013.

17 FDA Approves Olysio (simeprevir) in Combination with Sofosbuvir for Genotype 1 Chronic Hepatitis C Infection (2014, Nov 5). Retreived from http://www.drugs.com/

18 SovaldiUSpackageinsert.http://www.acessdata.fda.gov/drugsatfda_docs/label/2014/204671s001lb1.pdf(accessed Dec 12 2014)

19 FDA's Clinical Pharmacology and Biopharmaceutics Review of sofosbuvir: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204671Orig1s000ClinPharmR.pdf (accessed Dec. 12. 2014)

20 AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed April 24, 2014

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