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## RESEARCH ARTICLE

# Current and Emerging Therapeutic Regimens for Patients with Chronic Hepatitis C Infection

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**Abstract:** With 5.2 million people living with Hepatitis C, it is the most common blood-borne infection in the United States. Untreated chronic HCV infection may result in adverse consequences such as cirrhosis, portal hypertension, hepatic failure and hepatocellular carcinoma. Previously approved treatments include Pegylated-interferon alpha-2a/2b plus ribavirin, Boceprevir and Telaprevir. Recently approved medications include Sofosbuvir (SOF), Simeprevir (SMV), Ledispavir-Sofosbuvir (Harvoni®) and Ombitasvir-paritaprevir-ritonavir with dasabuvir tablets (Viekira Pak). Here we review the literature describing the current and emerging therapies for chronic hepatitis C.

**Keywords:** Chronic, Direct acting antiviral agents, Hepatitis C, Treatment.

## INTRODUCTION

The hepatitis C virus (HCV) has become the most common blood-borne infection in the United States (USA) [1]. Studies show that there are now about least 5.2 million people in the USA living with HCV [2]. Untreated chronic HCV (CHC) infection can lead to adverse consequences such as portal hypertension, hepatocellular carcinoma, cirrhosis, and hepatic failure. This had led to extensive research to study the disease, its complications and potential treatment regimens. Various studies were performed in recent years on different treatment options of HCV. These include interferon alpha (IFN- $\alpha$ ) [3 - 12], Pegylated-interferon alfa-2a (PegIFN- $\alpha$ 2a) by itself or in combination with ribavirin (RBV) as well as Pegylated-interferon alfa-2b (PegIFN- $\alpha$ 2b) plus RBV [13, 14]. Other studies showed that the addition of protease inhibitors such as Boceprevir or Telaprevir to standard therapy with PegIFN and RBV improved rates of sustained virologic responses (SVR) in adults infected with previously treated and untreated HCV genotype 1 [15 - 18]. The US Food and Drug Administration (FDA) approved new medications for the treatment of HCV in 2013, Sofosbuvir (SOF) and Simeprevir (SMV). In October 2014, Ledipasvir-Sofosbuvir combination therapy (Harvoni®) was approved by FDA as the first treatment for genotype 1 chronic HCV infection to require only a daily single tablet regimen. Most recently, Ombitasvir-paritaprevir-ritonavir with dasabuvir tablets (Viekira Pak) was approved by FDA to treat those with chronic genotype 1 HCV regardless of status of cirrhosis. This article reviews the clinical trials that led to the development of approved protocols of these four medications.

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## Mechanism of Action of Therapy for HCV Infection

Understanding Hepatitis C virus structure and mechanism of replication is the key to appreciate how the new medications function in treatment of chronic HCV infection. Past research studies have attempted to explain and define the virus's life cycle in order to develop therapies for HCV infection by targeting key steps of its replication. Hepatitis C is a positive-strand RNA virus which encodes a polyprotein that undergoes proteolytic cleavage to other polypeptides. Two envelope glycoproteins and the core protein comprise the virus's structural proteins. Viral replication, post-replication assembly, and secretion processes are initiated when the non-structural (NS) proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B form a complex with viral RNA [19]. Inhibition of HCV replication can be achieved using interferon alfa (IFN- $\alpha$ ), which acts by inducing interferon-stimulated host genes containing antiviral functions. Ribavirin (RBV), a key component of treatment of HCV, works through 4 different pathways: (1) directly inhibits the replication of HCV, (2) inhibits the host inosine monophosphate dehydrogenase (IMPDH) enzyme, (3) induces the mutagenesis of the rapidly replicating virus beyond the threshold to error catastrophe, and (4) promotes immunomodulation by inducing a Th1 immune response. It is unclear, however, which one of these mechanisms predominates during ribavirin's synergistic action with interferon-alfa [20].

These NS proteins, which coordinate the intracellular processes of the virus' life cycle, have served as targets for recently developed medications to disrupt key steps in the replication of HCV. In particular, Telaprevir and Boceprevir are the 2 direct-acting antiviral agents that inhibit the NS3/4A serine protease which cleaves the HCV glycoprotein [21]. The NS5B is an RNA polymerase involved in the synthesis of the RNA genome of HCV. Two classes of drugs; Nucleotide inhibitors (NIs) and non-nucleotide inhibitors (NNIs) target the NS5B enzyme resulting in early chain termination and restriction of its activity, respectively [19]. The newly FDA approved drugs are Sofosbuvir (SOF; Sovaldi™, Gilead Sciences), an NI NS5B inhibitor, Simeprevir (SMV; Olysio™, Janssen), an NS3/4A protease inhibitor, and Ledipasvir (GS-5885, Gilead Sciences) an NS5A inhibitor [22, 23]. The most recently FDA approved regimen (Viekira Pak) consists of paritaprevir (ABT-450), an NS3/4A inhibitor combined with ombitasvir (ABT-267), an NS5A inhibitor and dasabuvir (ABT-333), a nonnucleoside NS5B RNA polymerase inhibitor [24].

### Sofosbuvir

Sofosbuvir (SOF), effectively treats chronic hepatitis C and was approved by FDA on December 6, 2013 as a component of an antiviral treatment regimen. This HCV nucleotide analog NS5B polymerase inhibitor has been evaluated as a treatment option of Genotype 1, 2, 3, 4 HCV infections through several clinical trials. The efficacy of SOF is also established in patients with hepatocellular carcinoma awaiting liver transplants, including patients who have HCV/HIV-1 co-infection [25 - 27].

## GENOTYPE 1 OR 4 CHC

### Treatment of Naïve Adults – NEUTRINO Trial

In the NEUTRINO trial, which was a single-arm, open-label trial with a 12-week treatment plan as outlined in Table 1. In this study, 327 subjects were included with mean body mass index (BMI) 29 kg/m<sup>2</sup> and a median age of 54 years. The baseline HCV RNA for 78% of subjects had greater than 6 log<sub>10</sub> IU per mL while 17% had cirrhosis. The study consisted of 78% of HCV subjects with genotype 1, 9% with genotype 4, and 2% with genotype 5 or 6. For 3 months starting from June 2012, patients were enrolled from 56 locations in the USA. Participants all received SOF 400mg once daily with weight-based RBV. Those patients weighing less than 75 kg, received 1000 mg daily and the other patients weighing 75 kg or more received 1200 mg daily. Once per week, PegIFN- $\alpha$ 2a was administered subcutaneously with a dose of 180  $\mu$ g. Two hundred and ninety-five of the 327 patients (90%) who participated in this study had a sustained virologic response (SVR) after 12 weeks of treatment. These results showed the superiority of SOF plus PegIFN-RBV when compared to the 60% ( $p < 0.001$ ) of an adjusted historical response rate. However, SVR didn't differ greatly among different HCV genotypes. SVR for genotype 1 was 89% (92% for genotype 1a and 82% for genotype 1b) vs 96% for those with HCV genotype 4 (Table 1). Race or ethnicity did not seem to substantially influence responses [25, 26].

## GENOTYPE 2 OR 3 CHC

### Treatment of Naïve Adults – FISSION Trial

The FISSION trial was a randomized, open label, active-control study with a study design as outlined in Table 1.

The FISSION trial enrolled from 97 sites in the United States, Italy, the Netherlands, Sweden, New Zealand, and Australia. Participants were randomized and stratified according to a 1:1 ratio by: (1) status of cirrhosis (presence or absence), (2) HCV genotype (2 vs. 3), and (3) HCV RNA level at baseline (<6 log<sub>10</sub> IU/mL vs. ≥ 6 log<sub>10</sub> IU/mL). Patients were enrolled in an approximately 1:3 ratio by genotype (2 vs. 3) with 72% of the subjects having HCV genotype 3. A total of 57% of treated subjects had baseline HCV RNA levels greater than 6 log<sub>10</sub> IU/mL and 20% of them had cirrhosis. The study showed that SOF-RBV was non-inferior to PegIFN-RBV at SVR<sub>12</sub>, the primary endpoint (SVR at 12 weeks after the end of therapy). Results also showed that of the patients receiving SOF, genotype 2 infected patients without cirrhosis were strongly associated with achieving high rates of SVR (Table 1) [25, 26].

**Table 1. Summary of major Trials leading to the FDA approval of Sofosbuvir; NEUTRINO, FISSION, POSITRON, FUSION, VALENCE Trials [25 - 28].**

Study	Patients	Treatment Regimen	Overall SVR
NEUTRINO	GT1, 4, 5 or 6 treatment naive	SOF + Peg-IFNα + RBV (12 weeks) (n=327)	90% (295/327)
FISSION	GT2&3 treatment naive	SOF + RBV (12 weeks) (n=256)	67% (171/256)
		Peg-IFNα + RBV (24 weeks) (n=243)	67% (162/243)
POSITRON	GT2&3 Peg-IFNα intolerant	SOF + RBV (12 weeks) (n=207)	78% (161/207)
FUSION	GT2&3 previously treated	SOF + RBV (12 weeks) (n=103)	50% (51/103)
		SOF + RBV (16 weeks) (n=98)	71% (70/98)
VALENCE	GT2&3 treatment naive and previously treated	Genotype 2 SOF + RBV (12 weeks) (n=73)	93% (68/73)
		Genotype 3 SOF + RBV (24 weeks) (n=250)	84% (210/250)

#### **Peg-Interferon-Ribavirin Intolerant, Ineligible or Unwilling Adults – POSITRON Trial**

The POSITRON trial was a randomized, double-blinded, placebo-controlled trial with a study design outlined in Table 1. Patients with and without cirrhosis were enrolled at 63 sites in the USA, New Zealand, Canada, and Australia starting on March 2012 for 3 months. Treated participants were at a median age of 54 years with about 54% male, 91% white, 5% African American and 11% Hispanic and Latino. A total of 70% had baseline HCV RNA levels greater than 6 log<sub>10</sub> IU per mL, 16% had cirrhosis, 49% had HCV genotype 3 where 9% were interferon intolerant, 44% were ineligible and 47% were unwilling. Eighty percent of the subjects didn't have any prior HCV treatment. Seventy-eight percent of those receiving SOF-RBV achieved a SVR at 12 weeks after treatment (95% confidence interval (CI), 72-83) while 0% of those in the placebo group ( $p < 0.001$ ) achieved SVR. Further analysis showed HCV genotype 3 having significantly higher association with reduced SVR rates when compared to HCV genotype 2 infection. Additionally, participants who had cirrhosis saw a lower association to SVR rates when compared to those without cirrhosis (Table 1) [25, 27].

#### **Previously Treated Adults – FUSION & VALENCE Trials**

The FUSION trial was a randomized, double-blinded, active-control trial with a study design as described in Table 1. In this trial, subjects were stratified by cirrhosis status (presence vs. absence) as well as HCV (genotype 2 vs. genotype 3). For 3 months starting on May 2012, enrollment came from 67 sites from the USA, New Zealand, and Canada. They were randomized to two treatment groups according to a 1:1 ratio; the first group included those receiving 12 weeks of treatment, followed by matching placebo for 4 weeks. The second group received treatment for 16 weeks instead. Participants were at a median age of 56 years with demographic characteristics of 70% male, 87% white, 9% Hispanic or Latino, and 3% African American. Additional characteristics included-mean BMI of 29 kg/m<sup>2</sup>, 73% of the subjects had baseline HCV RNA levels greater than 6 log<sub>10</sub> IU per mL, 34% had cirrhosis, 63% of subjects had HCV genotype 3, and 75% had previous treatment relapsed. The rate of SVR for subjects receiving SOF and RBV was better to the 25% historical control rate, with the 12-week group achieving a rate of 50% (95% CI, 40-60) ( $p < 0.001$ ) and the 16-week group achieving a rate of 73% (95% CI, 63-81) ( $p < 0.001$ ). The SVR was also noted to be higher in the 16-week group compared to those in the 12-week group (difference, -23 percentage point; 95% CI, -35 to -11;  $p < 0.001$ ). Similar to POSITRON, lower SVR was seen in patients who had cirrhosis, particularly among HCV genotype 3 (Table 1) [25, 27].

Originally a multicenter phase 3 trial, the VALENCE trial randomly assigned participants according to a 4:1 ratio to receive either SOF-RBV or placebo and had a study design as outlined in Table 1. Subjects were stratified according to not receiving previous therapy *versus* not receiving previous therapy as well as whether or not patients had cirrhosis at

screening. The initial plan was to treat the subjects with a 12-week course of SOF-RBV or placebo. However, the design of the study was modified after the results of the FUSION trial was published suggesting that patients may benefit in their treatment of HCV genotype 3 by extending treatment further than 12 weeks. Therefore, the study-group assignments of the VALENCE trial were unblinded with the placebo group being discontinued. No change was made to the treatment regimen for HCV genotype 2 patients receiving treatment for 12 weeks, but those with HCV genotype 3 had their treatment extended from 12 to 24 weeks. In this study, the treated participants had the following demographic characteristics: median age of 51 years, 60% male, mean BMI of 26 kg/m<sup>2</sup>, mean baseline HCV RNA level of 6.4 log<sub>10</sub> IU per mL. In this trial, 78% of subjects had HCV genotype 3; 21% had cirrhosis, and 58% of participants received previous treatment for HCV with 65% of those participants had a relapse/breakthrough prior to treatment. Among participants with HCV genotype 2 who also received SOF-RBV for 12 weeks, 93% (9% CI, 85-98) achieved SVR 12 weeks after treatment cessation; among those, some still had SVR for 24 weeks after treatment. In the genotype 3 group receiving SOF-RBV for 24 weeks, 85% (95% CI, 80-90) achieved SVR 12 weeks after treatment cessation, and most of those (206 out of 213), maintained SVR for 24 weeks after treatment. Further analysis of those with HCV genotype 2 infections, SVR rates were consistently high across subgroups. The SVR rates of participants with HCV genotype 3, however, varied according to the history of treatment as well as whether or not they had cirrhosis. Among patients not previously treated, patients with and without cirrhosis achieved rates of SVR of 92% and 95%, respectively. Additionally, among the previously treated HCV genotype 3 patients, rates of SVR were at 62% with cirrhotic patients and 87% with non-cirrhotic patients (Table 1) [25, 28].

### Adverse Reactions

Common adverse events (AE) for SOF plus RBV combination include fatigue and headache. Common AE for SOF plus PegIFN- $\alpha$ /RBV combination therapy include fatigue, headache, nausea, insomnia and anemia [25]. These AE were consistent among the NEUTRINO, FISSION, POSITRON, FUSION, and VALENCE trials.

### HCV and HIV Co-infection: PHOTON-1 Trial

The PHOTON-1 trial was a multicenter, open label, non-randomized, uncontrolled phase 3 trial which attempted to determine the rates of SVR and adverse event in people with HCV and HIV co-infection receiving both SOF and RBV. Subjects enrolled in the study through 34 academic, community health centers, and private practice in Puerto Rico and the USA for 8 months starting from August. Patients had a co-infection of HCV genotype 1, 2 or 3 and HIV. Two different groups of people were enrolled: the first group included those patients receiving anti-retrovirus treatment (ART). This group of patients was required to have a CD4 count greater than 200 and HIV RNA values less than 50. The second group was patients not being treated with ART, with CD4 count greater than 500. For 12 weeks, treatment-naïve participants with HCV genotype 2 or 3 received 400mg of SOF and weight-based RBV. Two kinds of patients (treatment-naïve with HCV genotype 1 and treatment-experienced with HCV genotype 2 or 3) had identical treatment regimens for 24 weeks. Additionally, analysis revealed high rates of SVR at 12 weeks (SVR<sub>12</sub>): 87 from 114 patients (95% CI, 67-84) with genotype 1, 23 out of 26 participants (95% CI, 70-98) with genotype 2, and 28 out of 42 patients (95% CI, 51-80) of patients with genotype 3. In treatment-experienced subjects, 22 out of 24 subjects (92%) with genotype 2 and 16 out of 17 patients (94%) achieved SVR<sub>12</sub>. These sets of results suggested that participants with HIV/HCV genotype 1, 2, or 3 coinfection achieved high SVR rates after 12 weeks of SOF-RBV combination treatment for 12 or 24 weeks. Common adverse events noted to be fatigue, insomnia, headache, and nausea [29].

### SIMEPREVIR

Simeprevir (TMC435; Janssen and Medivir) is an HCV NS3/4A protease inhibitor already approved for consumption in several countries including Japan, Canada, Russia, Europe and USA to treat participants with chronic HCV. Simeprevir (SMV) has broad genotypic coverage with antiviral activity against HCV genotypes 1, 2, and 4-6. Simeprevir acts by inhibiting the protease mediated cleavage of several of the non-structural proteins of HCV from the polypeptide encoded by the viral genome [30 - 32]. Several trials have studied the effectiveness of SMV in people with chronic HCV which have led to the current recommendations.

### Genotype 1

#### *Genotype 1, Treatment-Naïve Patients; QUEST-1, QUEST-2, CONCERTO-1, PILLAR, DRAGON Trials*

Several trials studied the safety and efficacy of SMV when combined with other medications in people with HCV

genotype 1 and had not been treated in the past. QUEST-1 was a phase 3, randomized, double-blinded, placebo-controlled multicenter trial that aimed to determine the efficacy, safety, and tolerability of SMV combined with PegIFN- $\alpha$  plus RBV (SMV group) versus placebo combined with PegIFN- $\alpha$  plus RBV (placebo group) in people with HCV genotype 1 infection. These treatment-naive patients were enrolled from 13 countries including New Zealand, Puerto Rico, Europe, Australia, and North America. Subjects were stratified by HCV subtype and host IL28B genotype and were randomly assigned to the SMV or placebo group according to a 2:1 ratio. Overall treatment duration in the SMV group was either 24 weeks or 48 weeks in accordance to the response-guided therapy criteria (including 12 weeks of dosing with SMV). The control group received placebo and PegIFN- $\alpha$  plus RBV for 48 weeks. SVR at 12 (SVR12) weeks after treatment was the primary efficacy endpoint. Treatment with SMV plus PegIFN- $\alpha$ 2a and RBV was at 80% at SVR12, which was better than the 50% of placebo plus PegIFN- $\alpha$ 2a and RBV with the adjusted difference 29.3% (95% CI 0.1-38.6;  $p < 0.001$ ). Adverse events such as anemia, headache, fatigue, and rash were similar between the two groups suggesting that SMV doesn't result in worsening of the adverse event profiles associated with PegIFN- $\alpha$ 2a plus RBV [33].

QUEST-2 was set up to be equal to the QUEST-1 trial with the notable exception of using PegIFN- $\alpha$ 2a and PegIFN- $\alpha$ 2b instead of PegIFN- $\alpha$ . Participants enrolled from 76 sites in 14 countries in South America, North America, and Europe. Participants were stratified by HCV genotype 1 subtype (1a, 1b, or other) and IL28B genotype (CC, CT, or TT). They were then randomized in a 2:1 ratio to the SMV or placebo group. For 12 weeks participants were treated with SMV (150 mg once daily PO), PegIFN- $\alpha$ 2a (180  $\mu$ g once weekly, subcutaneous injection) or PegIFN- $\alpha$ 2b (weight-based once weekly) plus RBV (1000-1200 mg daily or 800-1400 mg daily PO; SMV group) or placebo (once daily PO), PegIFN- $\alpha$ 2a or 2b, plus RBV (placebo group), followed by a 12 or 48-week regimen of either PegIFN- $\alpha$ 2a or PegIFN- $\alpha$ 2b plus RBV (SMV group) based on the criteria for response-guided therapy or 48 weeks (placebo). SVR12, the primary endpoint, was achieved by 209 (81%) of 257 of those receiving SMV and 67 (50%) of 134 receiving placebo (95% CI 23.3-41.2;  $p < 0.001$ ). SMV and placebo groups had similar incidence of adverse events at 12 weeks suggesting that addition of SMV to either PegIFN- $\alpha$ 2a or PegIFN- $\alpha$ 2b plus RBV improved SVR in study participants [34].

CONCERTO-1 was similar to the study characteristics of QUEST-1 and QUEST-2 and enrolled the same kinds of participants to study the safety and efficacy of SMV combined with PegIFN- $\alpha$ 2a plus RBV (PegIFN $\alpha$ /RBV). Patients were stratified by age ( $< 65$  or  $\geq 65$ ) and IL28B genotype (rs8099917; TT, TG and GG), and randomized according to a ratio of 2:1 to SMV 100mg daily plus PegIFN $\alpha$ /RBV for 12 weeks. Participants were then placed to a response-guided therapy (RGT) with PegIFN $\alpha$ /RBV alone for 12 or 36 weeks, or they were given placebo with PegIFN $\alpha$ /RBV for 12 weeks then PegIFN $\alpha$ /RBV for 36 weeks. For this trial, the SVR12 rates was at 88.6% in the SMV-treated group and 61.7% in the placebo group ( $p < 0.0001$ ), with lower viral relapse rates in SMV-treated group. The overall adverse event profile among the two groups were comparable [35].

PILLAR and DRAGON trials were two smaller studies, both studied the safety and efficacy of SMV when added to PegIFN- $\alpha$ 2a and RBV in treatment-naive participants with HCV genotype 1. Both trials demonstrated significantly higher SVR when SMV was added to PegIFN- $\alpha$ 2a and RBV compared with PegIFN- $\alpha$ 2a and RBV alone. DRAGON trial also showed Lower relapse rates in SMV -treated patients compared to patients only receiving PegIFN- $\alpha$ 2a-RBV. The safety profiles between the 2 groups were similar [36, 37].

#### ***Genotype 1, Patients with Treatment-failure (Non-responders); ASPIRE Trial***

ASPIRE trial was a phase 3, randomized, placebo-controlled, double-blind trial which investigated the safety and efficacy of the combined treatment of SMV, PegIFN- $\alpha$ 2a, and RBV in HCV genotype 1 participants who have failed prior treatment with only PegIFN and RBV. This study showed significantly higher SVR24 rates in the groups given SMV compared to placebo group (61%-80% vs. 23%;  $p < 0.001$ ), regardless of past treatment response using PegIFN and RBV (Table 2). All groups had comparable numbers of adverse events [39].

#### ***Genotype 1, Patients with Relapse; PROMISE Trial***

PROMISE had the same study characteristics as the ASPIRE trial to investigate the same study drugs. The PROMISE trial also enrolled similar patients to that of ASPIRE but instead relapsed after interferon-based therapy. PROMISE enrolled from 14 countries across Asia-Pacific region, Europe, and North America. Participants were stratified by HCV 1 subtype (1a, 1b, and other) and IL28B genotype (rs12979860; CC, CT, or TT). They were randomized according to a ratio of 2:1 to be treated with either SMV (150mg PO daily) plus PegIFN- $\alpha$ 2a-RBV (180 $\mu$ g weekly and 1000 or 1200mg daily depending on body weight, respectively) or placebo plus PegIFN- $\alpha$ 2a for 12 weeks.

Patients received PegIFN- $\alpha$ 2a and RBV (PR) for 12 or 36 weeks (SMV group, based on response-guided therapy criteria), while the rest were in the placebo group for 36 weeks. SMV and PR were significantly better to the treatment of placebo and PR, and the SVR12 rates were 79.2% versus 36.1%, respectively (95% CI, 34.6-53.0;  $p < 0.001$ ). Participants receiving SMV and PR saw treatment failure rates and relapse rates lower than those who received placebo and PR. The prevalence of adverse events among both groups were similar suggesting that in HCV genotype 1 participants who relapsed after treatment with interferon tolerated the addition of SMV to PR with superior SVR12 [40].

**Table 2. Treatment outcome in adult subjects with HCV genotype 1 infection who failed prior peg-IFN-alfa and RBV therapy (ASPIRE trial, prior partial and null responders) [38, 39].**

Treatment Outcome		150 mg SMV 12 Weeks + PR N=66% (n/N)	Pooled 100 mg and 150 mg SMV 12 Weeks + PR N=132% (n/N)	Placebo + PR N=66% (n/N)	
SVR24	Prior relapser	77 (20/26)	83 (44/53)	37 (10/27)	
	Prior partial responders	65 (15/23)	67 (31/46)	9 (2/23)	
	Prior null responders	53 (9/17)	45 (15/33)	19 (3/16)	
Outcome for all subjects without SVR24	On-treatment virologic failure*	Prior relapser	8 (2/26)	6 (3/53)	22 (6/27)
		Prior partial responders	22 (5/23)	20 (9/46)	78 (18/23)
		Prior null responders	35 (6/17)	36 (12/33)	75 (12/16)
	Viral Relapse†	Prior relapser	13 (3/23)	8 (4/49)	47 (9/19)
		Prior partial responders	6 (1/17)	8 (3/36)	50 (2/4)
		Prior null responders	18 (2/11)	20 (4/20)	25 (1/4)

150 mg SMV: 150 mg SMV for 12 weeks with Peg-IFN- $\alpha$ 2a and RBV for 48 weeks; Placebo: placebo with Peg-IFN- $\alpha$ 2a and RBV for 48 weeks. SVR24: sustained virologic response 24 weeks after planned end of treatment (EOT).

\* On-treatment virologic failure was defined as the proportion of subjects who met the protocol-specified treatment stopping rules (including stopping rule due to viral breakthrough) or who had detectable HCV RNA at EOT (for subjects who completed therapy).

† Viral relapse rates are calculated with a denominator of subjects with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment.

### HCV/HIV Co-infection

SMV's safety and efficacy was investigated in patients with HCV genotype-1/HIV-1 co-infection in an uncontrolled, open-label trial, phase 3 study. Participants received a 12-week regimen of SMV (150mg QD) with PegIFN- $\alpha$ 2a /RBV (PR). Response-guided therapy (RGT) with PR was given to prior relapsers and to non-cirrhotic HCV treatment-naïve subjects for 24 or 48 weeks. Patients who previously were non-responders, partial responders, and were cirrhotic were treated with PR for 48 weeks. Treatment-naïve patients saw SVR12 rates at 79.2%, past non-responders saw a rate of 57.1%, previous relapsers saw a rate of 86.7% for, and previous partial responders saw a rate of 70.0%. Out of the eligible 85% of participants meeting RGT criteria for 24 weeks of PR, 87% of those people achieved SVR12. SMV and PR therapy had common adverse events such as headache, fatigue, nausea and neutropenia, suggesting that SMV was well-tolerated, similar to that of HCV mono-infected participants. Additionally, rates of SVR12 were high in the treatment-naïve, past relapsers, past partial responders, and previous null responders with HIV-1 co-infection [41].

### SIMEPREVIR (SMV) PLUS SOFOSBUVIR (SOF); COSMOS TRIAL

The COSMOS trial investigated the combined efficacy of SMV and SOF in people with chronic HCV genotype 1 who either never received treatment or were non-responders to previous interferon therapy. In this trial, participants were assigned randomly to 4 groups according to a ratio of 2:2:1:1 with all groups receiving 150mg SMV and 400 mg SOF daily with some key differences in time period or addition of RBV: group 1 received 24 weeks with RBV, group 2 received 24 weeks without RBV, group 3 received 12 weeks with RBV, or group 3 received 12 weeks without RBV. Additionally, all were categorized according to two cohorts: (1) prior non-responders with METAVIR scores F0-F2 and (2) prior non-responders and treatment-naïve patients with METAVIR scores F3-F4. SVR at 12 weeks after treatment (SVR12) was the primary endpoint. Ninety-two percent of participants in cohort 1 achieved SVR12 while 94% of participants in cohort 2 reached that endpoint. It suggests that combined SMV and SOF was efficacious in treatment of these groups of patients. Fatigue (52%), headache (20%), and nausea (16%) were the common adverse events with the groups pooled together [23].

### LEDISPAVIR PLUS SOFOSBUVIR (HARVONI®)

Ledipasvir (GS-5885, Gilead Sciences) is a new HCV NS5A inhibitor that has exhibited potent antiviral activity in patients with HCV genotypes 1a and 1b. In a phase 1, randomized, placebo-controlled, 3 day mono-therapy, Ledipasvir (LDV) was well tolerated and resulted in significant antiviral activity in HCV genotype 1a and 1b participants. Several trials investigated Ledipasvir's efficacy combined with SOF in people with HCV genotype 1. In fact, on October 10th, 2014, the first combination pill, Harvoni (LDV plus SOF), was approved by the FDA to treat HCV genotype 1 infection [42].

#### Genotype 1, Treatment Naive Patients; ION-1, ION-3 Trials

ION-1 trial was phase 3, open label, randomized, multicenter study which evaluated the efficacy of the once daily dose of LDV-SOF in treatment-naive patients with HCV genotype 1. Participants in this study were assigned randomly according to a 1:1:1:1 ratio to 4 groups and each group received one the following treatments regimens: (1) LDV-SOF in a fixed-dose combination tablet once daily for 12 weeks, (2) ledipasvir-SOF plus RBV for 12 weeks, (3) ledipasvir-SOF for 24 weeks, (4) or ledipasvir-SOF plus RBV for 24 weeks. Achieving SVR at 12 weeks after treatment (SVR12) was the primary endpoint. The SVR rates were 99% (95% CI 96-100) in the group first group, 97% (95% CI, 94-99) in the second group, 98% (95% CI, 95-99) in the third group and 99% (95% CI, 97-100) in the fourth group suggesting that once-daily LDV-SOF was highly effective in participants who were treatment-naive patients and had HCV genotype 1 regardless of RBV or time period of treatment (Table 3) [43].

**Table 3. Response during and after treatment-ION-1 trial [43].**

Response	12-Wk regimen		24-Wk regimen	
	LDV-SOF (N=214)	LDV-SOF+RBV (N=217)	LDV-SOF (N=217)	LDV-SOF+RBV (N=217)
<b>HCV RNA &lt;25 IU/ml</b>				
<b>During treatment-no./total no. (%)*</b>				
At week 2	174/213 (82)	181/217 (83)	179/216 (83)	180/217 (83)
At week 4	213/213 (100)	215/217 (99)	216/216 (100)	217/217 (100)
At week 12	213/213 (100)	214/214 (100)	213/214 (>99)	216/216 (100)
<b>After end of treatment-no. (%)</b>				
At week 4	211 (99)	213 (98)	215 (99)	215 (99)
At week 12	211 (99)	211 (97)	212 (98)	215 (99)
<b>Virologic failure during treatment-no.</b>	0	0	1	0
<b>Relapse-no.</b>	1	0	1	0
<b>Lost to follow up-no.</b>	2	4	2	2
<b>Withdrew consent-no.</b>	0	2	1	0

\*Data shown by authors of ION-1 trial for patients for whom HCV RNA results were available

In ION-3 trial, a phase 3, open-label, multi-center, randomized trial that had a shorter treatment duration (8 weeks) of LDV-SOF. In this study, people with HCV genotype 1 who were treatment-naïve and without cirrhosis were randomly assigned to receive LDV-SOF for 8 weeks, LDV-SOF plus RBV for 8 weeks, or LDV-SOF for 12 weeks. The primary end point for this trial was also SVR12. The SVR was 94% (95% CI, 90-97) for first group, 93% (95% CI, 89-96), for second group and 95% (95% CI, 92-98) for the third group which suggested noninferiority of the 8-week LDV-SOF treatment plan compared to a noninferiority margin of 12 percentage points. There was no notable benefit seen when including RBV or by prolonging the regimen into a 12-week regimen among non-cirrhotics [44].

Similar results were found in LONESTAR trial which was an open label, randomized, phase 2 trial in which its results showed that a fixed-dose of SOF-LDV alone or combined with RBV can potentially cure people with genotype 1 HCV, regardless of the presence of any prior treatments or cirrhosis [45].

#### Genotype 1, Patients with Treatment-failure; ION-2 Trial

ION-2 trial was an open-label, phase 3, randomized trial investigating the efficacy of Ledipasvir-SOF combination therapy in patients who were not able to achieve an expected SVR using prior interferon-based treatment with a genotype 1 HCV infection. In this study, patients were stratified according to their status of cirrhosis (presence vs. absence), genotype (1a vs. 1b), and responses to past therapies (relapses or virologic breakthroughs vs. no response) and received a random assignment according to a 1:1:1:1 ratio to one of the four groups for treatment: (1) LDV-SOF for 12

weeks, (2) LDV-SOF with RBV for 12 weeks, (3) LDV-SOF for 24 weeks, (4) or LDV-SOF with RBV for 24 weeks. Participants received a combination, fixed-dose tablet with 90 mg of LDV and 400mg of SOF PO daily and RBV. SVR12 was the primary endpoint for this study. Rates of SVR were high across these groups: 94% (95% CI, 87-97) for the first group, 96% (95% CI, 91-99) in second group, 99% (95% CI, 95-100) in both the third group and fourth group. Adverse events that were common across all groups were nausea, headache, and fatigue. The results suggested that the treatment with a regimen of a once daily, single tablet of LDV-SOF saw high SVR rates among participants with genotype 1 HCV who received prior interferon based treatments but did not achieve SVR [46].

#### ABT-450/r-OMBITASVIR and DASABUVIR (VIEKIRA PAK)

Recently in December 2014, Viekira Pak, an interferon-free combination therapy (ritonavir, paritaprevir, ombitasvir, and ritonavir tablets combined with dasabuvir tablets) was approved by the FDA to treat people with chronic genotype 1 HCV with or without cirrhosis [24]. Several trials preceded the approval of this regimen (Table 4).

**Table 4. Summary of major Trials preceding the FDA approval of Viekira Pak; PEARL-II, PEARL-III, PEARL IV, TURQUOISE-II, SAPPHIRE-I, SAPPHIRE-II Trials\* [24, 47 - 50].**

Study	Patients	Treatment Regimen	Overall SVR
PEARL-II (12 weeks)	GT1b previously treated (n=175)	Viekira Pak+RBV (n=88)	97% (85/88)
		Viekira Pak only (n=91)	100% (91/9)
PEARL-III (12 weeks)	GT1b treatment-naïve (n=419)	Viekira Pak+RBV (n=210)	99% (209/210)
		Viekira Pak only (n=209)	99% (207/209)
PEARL-IV (12 weeks)	GT1a treatment-naïve (n=305)	Viekira Pak+RBV (n=100)	97% (97/100)
		Viekira Pak only (n=205)	90% (185/205)
TURQUOISE-II (12 & 24 weeks)	GT1 treatment-naïve and previously treated with compensated cirrhosis (n=380)	Viekira Pak+RBV, 12 weeks (n=208)	92% (191/208)
		Viekira Pak+RBV, 24 weeks (n=172)	96% (165/172)
SAPPHIRE-I (12 weeks)	GT1 treatment-naïve (n=631)	Viekira Pak+RBV (n=473)	96% (455/473)
SAPPHIRE-II (12 weeks)	GT1 previously treated (n=394)	Viekira Pak+RBV (n=297)	96% (286/297)

\*Table was retrieved from online source with minor changes [50].

#### Genotype 1, Treatment Naïve Patients; SAPPHIRE-1, PEARL-III and PEARL-IV Trials

SAPPHIRE-1 trial was a phase 3, international, multicenter, placebo-controlled, double-blind, randomized trial that aimed to assess the safety and efficacy of combination therapy for 12 weeks with protease inhibitor ABT-450 (paritaprevir) with ritonavir (ABT-450/r) and ombitasvir plus dasabuvir and RBV. In this study, eligible patients were treatment-naïve, non-cirrhotic, ages 18-70 years, infected with genotype 1 HCV, and had a plasma HCV RNA level of more than 10,000 IU per milliliter. Participants were assigned randomly according to a 3:1 ratio and placed into either the treatment group (group A) or placebo group (group B) and were randomized by their HCV genotype (1a vs. non-1a) and their IL28B genotype (CC vs. non-CC). Those in group A received treatment for 12 weeks for once a day dose of co-formulated ABT-450/r-ombitasvir (150mg of ABT-450, 100mg of ritonavir, and 25mg of ombitasvir) and dasabuvir (250mg twice daily) with a twice daily, weight-based dose of RBV (1000mg if patient weighed <75kg or 1200mg if patient weighed ≥75). Group B received matching placebos. SVR12 was the primary end point for this study. A total of 631 participants throughout the trial received at least one dose of treatment. SVR12 rates for group A was superior and noninferior to the historical control rate of telaprevir plus PegIFN-RBV, additionally it was found to be 96.2% (95% CI, 94.5-97.9). Participants in group A with HCV genotype 1a and genotype 1b had response rates of 95.3% 98.0%, respectively. The occurrence of adverse events (asthenia, diarrhea, insomnia, pruritus, and nausea) were more significant among participants in group A compared with group B ( $p < 0.05$ ). These results suggested that non-cirrhotic, treatment-naïve people with genotype 1 HCV had a high rate of SVR with a 12-week treatment plan of ABT-450/r-ombitasvir with dasabuvir and RBV [24].

PEARL-III and PEARL-IV were both phase 3 trials examining the safety and efficacy of ABT-450/r-ombitasvir and dasabuvir regimen with and without RBV in HCV genotype 1 patients who were treatment-naïve, and non-cirrhotic. A total of 724 participants, 419 with HCV genotype 1b (PEARL-III) and 305 with genotype 1a (PEARL-IV), were assigned randomly to either a 12 week treatment of ABT-450/r-ombitasvir-dasabuvir and weight based RBV or to a matching placebo for RBV. Results of these two trials showed that treatments of a 12-week regimen with ABT-450/r-ombitasvir and dasabuvir but no RBV was associated with high SVR12 rates in participants who had HCV genotype 1 and were treatment-naïve. HCV genotype 1a participants who were previously treated demonstrated higher rates of virologic failure among those who did not receive RBV compared to ones who were also treated with RBV. These



findings were not demonstrated among people with HCV genotype 1b infection [47].

### **Genotype 1, Previously Treated Patients; SAPHIRE-2 Trial**

SAPHIRE-2 was a multi-center, international, randomized, double-blind trial. This study had non-cirrhotic patients with HCV genotype 1 and plasma HCV RNA levels of more than 10,000 IU per milliliter enrolled if they had been previously treated with PegIFN-RBV. This study's double blind treatment regimen lasted for a 12-week period. Participants were assigned randomly according to a ratio of 3:1 and received a daily dose of coformulated ABT-450/r-ombitasvir (150mg of ABT-450, 100mg of ritonavir, and 25mg of ombitasvir) with the addition of a twice daily dose of dasabuvir (250mg) and weight-based RBV (1000 or 1200mg daily). The control group received matching placebos for the 12 weeks. SVR12 was the primary endpoint. An overall SVR rate of 96.3% (95% CI, 94.2-98.4) was found in the active regimen group consisting of 286 of the 297 patients at week 12 post-treatment, which was better than the historical control rate. Rates of SVR12 were 95.3% in those who experienced previous relapses, 100% in those who experienced previous partial responses, and 95.2% in those who experienced previous null responses to PegIFN-RBV. Overall, the 12-week course of Viekira Pak with RBV saw a response amounting to more than 95% in participants with genotype 1 HCV who received PegIFN-RBV dual therapy and failed [48 - 50].

### **Genotype 1, Patients with Cirrhosis; TURQUOISE-II Trial**

TURQUOISE II was an open-label, international, phase 3, randomized trial studying the efficacy and safety of coformulated ABT-450/r-ombitasvir and dasabuvir with ribavirin for a 12 or 24-week treatment regimen. Patients enrolled in the study compared adults with genotype 1 HCV who were treatment-naïve and were previously treated with compensated cirrhosis. Eligible participants needed to have: (1) proof of cirrhosis either through a liver biopsy or by FibroScan, (2) a Child-Pugh class A score of <7 at screening, and (3) no past or current evidence of Child-Pugh class B or C disease. Only patients with platelet count of 60,000 per cubic millimeter or more, a serum albumin level of 2.8g per deciliter or more, bilirubin levels of less than 3mg per deciliter, a 2.3 ratio or less of an international normalized (INR), and a level of 100ng per milliliter or less of serum alpha-fetoprotein (AFP) were included. Exclusion criteria included those with a previous therapy of directly acting antiviral agents (*e.g.* telaprevir and boceprevir) and a hepatocellular carcinoma diagnosis. Three hundred and eighty participants who had Child-Pugh class A cirrhosis were treated with ABT-450/r-ombitasvir with dasabuvir and weight based RBV for 12 or 24 weeks with SVR12 as the primary endpoint. Those who achieved SVR12 in each group were compared with the estimated rate with a telaprevir-based regimen. The rate of SVR for 191 of the 208 patients receiving 12 weeks of treatment was 91.8% (97.5% CI, 87.6-96.1). The rate of SVR for 165 of the 172 participants who received a treatment of 24 weeks was 95.9% (97.5% CI, 92.6- 99.3), which was superior to the historical control rate. This study showed high SVR rates in cirrhotic participants with genotype 1 HCV receiving this new multitargeted, interferon-free regimen [51].

Currently, the FDA has approved the treatment of people with genotype 1 HCV with Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets co-packaged with dasabuvir tablets), regardless if they have cirrhosis. Viekira Pak is able to be used with or without RBV, however using RBV is not recommended by FDA for patients with decompensated cirrhosis [51].

### **FINAL REMARKS AND FUTURE TREATMENTS**

Treatment of chronic hepatitis C has evolved rapidly in the past few years. In the past year, four new medications have been approved by FDA; Sofosbuvir, Simeprevir, Harvoni and Viekira Pak. There are several other trials currently in progress that aim to develop new treatment options with better safety profile. Despite efforts, there are no FDA approved regimens for HCV genotype 5 and 6 or any specific dosage recommendations for patients with HCV/HIV co-infection. As current healthcare systems are making every effort to save costs, one may hope to advance the current treatment of chronic HCV not only efficiently and safely but also in a cost-effective manner.

### **CONFLICT OF INTEREST**

The authors confirm that this article content has no conflict of interest.

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