UPDATE:
New Hepatitis C Combination Agents

Ledipasvir and Sofosbuvir (Harvoni®)
Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir (Viekira Pak®)

Final Report
July 2015

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Executive Summary

Introduction: Treatment of hepatitis C virus (HCV) is extensive and requires long-term (up to 48 weeks) treatment with two to three agents. Currently, there are nine agents available for the treatment of HCV including: boceprevir, Harvoni®, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, simeprevir, sofosbuvir, telaprevir and Viekira Pak®. Ledipasvir/sofosbuvir (Harvoni®) and ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®) are the two newest agents approved for use in the treatment of HCV. These agents are available in oral combination tablet forms and are indicated in the treatment of HCV in patients with genotype 1 infection.

Hepatitis C virus is the most common chronic bloodborne disease in the United States. Clinical features associated with HCV infection range from asymptomatic to debilitating disease or even liver failure. Treatment options available for chronic hepatitis C have expanded in the previous two decades and the development of new direct-acting antiviral agents has proven beneficial in patients who were previously resistant to interferon combination therapy, including those with genotype 1. The use of protease inhibitors and/or nucleotide analogue inhibitors, like dasabuvir, ledipasvir, ombitasvir or sofosbuvir, in combination or in addition to ribavirin therapy has demonstrated improvements in treatment responses in patients previously resistant to standard therapy.

Clinical Efficacy: Seven clinical trials evaluating the efficacy of ledipasvir/sofosbuvir combination therapy and six clinical trials evaluating the efficacy of ombitasvir/paritaprevir/ ritonavir/dasabuvir combination therapy are available for evaluation. Overall, the evidence suggests these combination therapies demonstrate efficacy in the treatment of hepatitis C genotypes 1 and produce sustained virologic response rates of ~80-100%. The combination therapies demonstrated efficacy in treatment-naïve and treatment-resistant patients with treatment durations ranging from 6-24 weeks.

Special Populations: Despite continued advances in pharmacologic treatment options for HCV, risk factors still exist which are associated with poor treatment outcomes, including black race, advanced liver fibrosis, cirrhosis, HCV genotypes 1 and 4, high baseline HCV viral loads and other genetic mutations. In these patient populations, particularly in HCV genotype 1 and patients with advanced disease, Harvoni® and Viekira Pak® demonstrate improved sustained viral responsiveness.

Adverse Drug Reactions: In addition to improving rates of efficacy, the newer HCV therapeutic agents allow for shorter treatment durations and easier to tolerate treatment courses. Overall, Harvoni® and Viekira Pak®are well-tolerated. The most common adverse events reported in clinical trials include fatigue, headache, insomnia and nausea. These interferon-free combination regimens are associated with reduced rates of adverse events (including influenza-like symptoms, fever, depression and hematologic events) and shorter treatment durations.

Summary: The decision to treat a patient with HCV is a complicated one which requires careful consideration of when to initiate treatment, how long to treat the patient and which therapeutic agents to use. The decision to initiate treatment is based on severity of disease and presence or absence of various laboratory markers. The decision for duration of treatment is based on the

hepatitis C genotype and other comorbidities present. The decision on which agents should be used is based on patient history and current medication regimen in addition to all of the previous factors.

Introduction

Hepatitis refers to a group of liver disorders characterized by hepatic inflammation and necrosis with varying causes and severities.[1-3] Causes of hepatitis include viral, bacterial, autoimmune or drug-induced. Viral hepatitis can be further divided into 5 groups: A, B, C, D and E. Viral hepatitis A and E are self-limiting and, in general, do not result in chronic disease. Viral hepatitis B, C and D are typically chronic diseases which require extensive treatments. Hepatitis C Virus (HCV), for example, requires up to 48 weeks of drug therapy. Current agents available for the treatment of HCV include: boceprevir (Victrelis®), peginterferon alfa-2a (Pegasys®), peginterferon alfa-2b (Pegintron®), ribavirin (Copegus®, others), simeprevir (Olysio®), sofosbuvir (Sovaldi®), telaprevir (Incivek®) and the combination agents: ledipasvir/sofosbuvir (Harvoni®) and ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®). This report will focus on a review of the clinical safety and efficacy of the two newest combination agents, Harvoni® and Viekira Pak®, in the treatment of HCV. These agents are available as oral tablets and treatment duration is based on indication and disease response.[4,5] See Table 1 for a summary of all the current therapies available for the treatment of HCV.

Table 1. Comparison of the Hepatitis C Agents[4,5]

Product	Route of Administration	Available Doses	Labeled Uses	Dose Range (mg), Adults	Dose Range (mg), Pediatrics	Generic Available
Antihepaciviral, Interferons (Anti-HCV)						
Peginterferon alfa-2a (Pegasys®; Pegasys® ProClick)	Subcutaneous	135 mcg/0.5 mL (0.5 mL) 180 mcg/0.5 mL (0.5 mL) 180 mcg/mL (1 mL)	**Chronic hepatitis B:** Treatment of adults with hepatitis B e antigen (HBeAg)-positive and HBeAG-negative chronic hepatitis B virus (HBV) infection **Chronic hepatitis C:** Treatment of patients with chronic HCV infection alone or in combination with ribavirin **Unlabeled Uses:** Treatment of chronic hepatitis C genotypes 1, 4, 5 or 6 in combination with ribavirin and an HCV polymerase inhibitor	**Chronic hepatitis B:** 180 mcg once weekly for 48 weeks **Chronic hepatitis C:** 180 mcg once weekly monotherapy or in combination with ribavirin Duration of therapy- Genotypes 1, 4: 48 weeks Genotypes 2, 3: 24 weeks Genotypes 5, 6: No dosing recommendations provided Coinfection with HIV: 48 weeks	**Chronic hepatitis C; Children ≥5 years:** Combination therapy: 180 mcg/1.73 m2 x body surface area once weekly (max: 180 mcg) Duration of therapy: Genotypes 1,4,5,6: 48 weeks Genotypes 2,3: 24 weeks	No
Peginterferon alfa-2b (Pegintron®; Peg-Intron® Redipen; Peg-Intron® Redipen Pak 4; Sylatron®)	Subcutaneous	50 mcg/0.5 mL 80 mcg/0.5 mL 120 mcg/0.5 mL 150 mcg/0.5 mL Sylatron: 296 mcg; 444 mcg; 888 mcg; 4 x 296 mcg; 4 x 444 mcg	**PegIntron:** Treatment of chronic hepatitis C in combination with ribavirin **Sylatron:** Adjuvant treatment of melanoma **Unlabeled Uses:** Treatment of chronic hepatitis C genotypes 1,4, 5 or 6 in combination with ribavirin and an HCV polymerase inhibitor	**Chronic hepatitis C:** Monotherapy: (Duration 1 year) Weekly dose: ≤45 kg: 40 mcg; 46-56 kg: 50 mcg; 57-72 kg: 64 mcg; 73-88 kg: 80 mcg; 89-106 kg: 96 mcg; 107-136 kg: 120 mcg; 137-160 kg: 150 mcg Combination therapy: (Duration 48 weeks) Weekly dose: <40 kg: 50 mcg; 40-50 kg: 64 mcg; 51-60 kg: 80 mcg; 61-65 kg: 96 mcg; 66-75 kg: 96 mcg; 76-80 kg: 120 mcg; 81-85 kg: 120 mcg; 86-105 kg: 150 mcg; >105 kg: 1.5 mcg/kg **Melanoma:** 6 mcg/kg/week for 8 doses, followed by 3 mcg/kg/week for up to 5 years	**Chronic hepatitis C; Children ≥3 years:** Combination therapy: 60 mcg/m2 once weekly Duration of therapy: Genotype 1: 48 weeks Genotypes 2 and 3: 24 weeks	No

Product	Route of Administration	Available Doses	Labeled Uses	Dose Range (mg), Adults	Dose Range (mg), Pediatrics	Generic Available
Antihepaciviral, Nucleosides (Anti-HCV)						
Ribavirin (Copegus®; Moderiba®; Rebetol®; Ribasphere®; Ribasphere® RibaPak; Virazole®)	Inhalation powder Oral Capsule Oral Solution Oral Tablet	Capsule: 200 mg Powder for nebulization: 6 g (20 mg/mL) Solution: 40 mg/mL (100 mL) Tablet: 200 mg, 400 mg, 600 mg	**Inhalation:** Treatment of respiratory syncytial virus (RSV) infections **Capsule:** Treatment of chronic hepatitis C in combination with interferon alfa 2b **Solution:** Treatment of chronic hepatitis C in combination with interferon alfa 2b in patients ≥3 years of age **Tablet:** Treatment of chronic hepatitis C in combination with interferon alfa 2b in patients ≥5 years of age **Unlabeled Uses:** Treatment of influenza A and B and adenovirus; chronic hepatitis C genotypes 1,4, 5 or 6 in combination with ribavirin and an HCV polymerase inhibitor Inhalation: Treatment for RSV in adult hematopoietic stem cell or heart/lung transplant recipients	**Chronic hepatitis C:** (Combination therapy only) Solution daily dose: <66 kg: 800 mg; 66 to 80 kg: 1000 mg; 81 to 105 kg: 1200 mg; >105 kg: 1400 mg daily (600 mg in the morning, 800 mg in the evening) for 24-48 weeks Capsule/Tablet; Genotype 1, 4 daily dose: ≤75 kg: 1000 mg; >75 kg: 1200 mg for 48 weeks Capsule/Tablet; Genotype 2, 3, coinfection with HIV daily dose: 800 mg for 24-48 weeks	**RSV:** Continuous aerosol administration of 20 mg/mL solution for 12-18 hours/day for 3-7 days. **Chronic hepatitis C; Children ≥3 years:** (combination with interferon alfa-2b) <47 kg: 15 mg/kg/day; 47 to 59 kg: 800 mg; 60 to 73 kg: 1000 mg; >73 kg: 1200 mg **Chronic hepatitis C; Children ≥5 years:** (combination with peginterferon alfa-2a): 23 to 33 kg: 400 mg; 34 to 46 kg: 600 mg; 47 to 59 kg: 800 mg; 60 to 74 kg: 1000 mg; ≥75 kg: 1200 mg Duration of therapy: Genotypes 2,3: 24 wks All other genotypes: 48 wks	Yes: capsule, tablet
Antihepaciviral, Protease Inhibitors (Anti-HCV)						
Boceprevir (Victrelis®)	Oral Capsule	200 mg	**Chronic hepatitis C:** Treatment of chronic hepatitis C genotype 1 in combination with peginterferon alfa and ribavirin	**Chronic hepatitis C:** Weeks 1-4: Peginterferon alfa and ribavirin combination Weeks 5-8: Add boceprevir 800 mg 3 times daily with continued peginterferon alfa and ribavirin Weeks 9-24 & > 24: continue or discontinue treatment based on HCV-RNA levels	The safety, efficacy, and pharmacokinetic profile of boceprevir in pediatric patients have not been studied.	No

Product	Route of Administration	Available Doses	Labeled Uses	Dose Range (mg), Adults	Dose Range (mg), Pediatrics	Generic Available
Simeprevir (Olysio®)	Oral Capsule	150 mg	**Chronic hepatitis C:** Treatment of genotype 1 chronic hepatitis C in combination with peginterferon alfa and ribavirin	**Chronic hepatitis C:** Weeks 1 to 12: Triple therapy: Simeprevir 150 mg once daily in combination with peginterferon alfa and ribavirin Weeks 13-23: Based on HCV-RNA levels at weeks 4 and 12: Discontinue Simeprevir and consider continued dual therapy Week 24: Based on HCV-RNA results at week 24: Continue or discontinue dial therapy	The safety and efficacy of simeprevir in children and adolescents less than 18 years of age have not been established.	No
Telaprevir (Incivek®)	Oral Tablet	375 mg	**Chronic hepatitis C:** Treatment of genotype 1 chronic hepatitis C in combination with peginterferon alfa and ribavirin	**Chronic hepatitis C:** Weeks 1-12: Triple therapy: Telaprevir 1125 mg twice daily in combination with peginterferon alfa and ribavirin Weeks 13-23 & > 24: Based on HCV-RNA results at weeks 4 and 12: Discontinue Telaprevir and consider continued dual therapy	The safety, efficacy and pharmacokinetic profile of telaprevir in pediatric patients have not been established.	No
Antihepaciviral, Polymerase Inhibitor (Anti-HCV)						
Sofosbuvir (Sovaldi®)	Oral tablet	400 mg	**Chronic hepatitis C:** Treatment of genotype 1, 2, 3, or 4 chronic hepatitis C in combination with ribavirin or with peginterferon alfa and ribavirin and those with HCV/HIV-1 coinfection **Unlabeled Uses:** Treatment of genotype 5 or 6 chronic hepatitis C	**Chronic hepatitis C:** 400 mg daily with concomitant ribavirin and with or without peginterferon alfa for 12-24 weeks based on genotype and/or clinical scenario	Safety and effectiveness of sofosbuvir in children less than 18 years of age have not been established.	No

Product	Route of Administration	Available Doses	Labeled Uses	Dose Range (mg), Adults	Dose Range (mg), Pediatrics	Generic Available
Antihepaciviral, Combination Agents						
Ledipasvir and Sofosbuvir (Harvoni®)	Oral tablet	Ledipasvir 90-Sofosbuvir 400 mg	Treatment of chronic hepatitis C (CHC) genotype 1 in adults	**Treatment-naive patients with or without cirrhosis or treatment-experienced patients without cirrhosis:** One tablet once daily for 12 weeks **Treatment-experienced patients with cirrhosis:** One tablet once daily for 24 weeks	Safety and effectiveness have not been established in pediatric patients.	No
Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir (Viekira Pak®)	Oral tablet*	Dasabuvir 250 mg, Ombitasvir 12.5 mg, Paritaprevir 75 mg, Ritonavir 50 mg *copackaged product: ombitasvir, paritaprevir, and ritonavir in a fixed-dose combination tablet; dasabuvir a separate, individual tablet	Treatment of genotype 1 chronic hepatitis C virus infection, with or without ribavirin, including those with compensated cirrhosis Limitations of use: Not recommended for use in patients with decompensated liver disease.	**Chronic hepatitis C:** Ombitasvir/paritaprevir/ritonavir tablet: Two tablets every morning for 12-24 weeks Dasabuvir: 250 mg twice daily for 12-24 week	Safety and effectiveness in pediatric patients less than 18 years of age have not been established.	No

Key: HCV-Hepatitis C Virus; HIV-Human immunodeficiency virus

Disease Overview

With over 3 million people infected, hepatitis C virus (HCV) is the most common chronic bloodborne disease in the United States.[1-3,6] Across the world, HCV infects over 180 million people (~3% of the global population) with the highest prevalence (>3.5%) in central and eastern Asia, North Africa, and the Middle East. HCV is transmitted through exposure to infected blood most commonly via transfusion or injectable drug use but may also be transmitted through occupational, perinatal, or sexual exposures. Up to 70% of those infected with HCV are asymptomatic or only have mild illness and up to 85% of those infected with HCV will develop chronic disease. Those who are unaware of being infected are a large source of disease transmission and are at risk for developing cirrhosis and other chronic liver diseases which may not be detected until decades after the initial infection.[1-3,6]

Clinical features associated with HCV infection range from asymptomatic to debilitating disease or even liver failure.[1-3] The most common symptom reported with hepatitis C infection is fatigue which may also be accompanied by upper right quadrant pain. Jaundice, glomerulonephritis and other immune-mediated diseases (Sjögren's syndrome, type-II diabetes mellitus, metabolic syndrome) may be reported with HCV infections. Elevations in aminotransferases (alanine aminotransferase (ALT), aspartate aminotransferase (AST)), alkaline phosphatase, serum bilirubin, albumin and clotting factors in addition to detection of autoantibodies may or may not occur with laboratory testing in patients with HCV. For this reason, HCV is often referred to as the "silent killer." Progression to severe liver disease occurs most frequently in patients with older age, longer duration of infection, concomitant liver disorders (alcoholic liver disease, chronic hepatitis B, α1 -antitrypsin deficiency), HIV infection and obesity. Early detection and treatment in these patients may serve to reduce the progression to severe liver disease and mortality.[1-3]

Treatment of hepatitis C virus is extensive and requires long-term (up to 48 weeks) treatment with two to three agents.[1-3] Deciding when to initiate treatment depends on severity of disease and presence or absence of various laboratory markers and comorbidities. In general, patients with chronic hepatitis C with moderate disease and evidence of fibrosis who have detectable HCV ribonucleic acid (RNA) are good candidates for antiviral therapy.[6] In patients with less severe disease, indications for treatment are less clear and close monitoring may be considered in place of antiviral therapy as progression to cirrhosis is less likely. On the other hand, patients with severe liver disease and cirrhosis are less likely to respond to treatment. Careful consideration of the risks and benefits of therapy should be considered before initiating treatment. Six different genotypes and over 90 subtypes of HCV have been detected. Although there is little evidence for linking genotype to differences in disease progression there is evidence demonstrating differences in treatment responses according to HCV genotype. Successful treatment response to standard treatment in patients with genotypes 1 and 4 are substantially lower than in patients with other genotypes. Seventy percent of those with HCV in the US are infected with genotype 1. Genotyping is recommended before selecting antiviral therapy for treatment of HCV.[1-3]

Previously, the standard of care for the treatment of HCV was the combination of pegylated interferon and ribavirin.[6] This combination appears to be much less effective than the

newer therapies, with reduced rates of sustained virologic responsiveness (SVR), especially in patients with HCV genotypes 1 and 4. Sustained virologic response is defined as the absence of viral markers 24 weeks after completion of antiviral therapy. A positive SVR is considered a clinical cure. Treatment options available for chronic hepatitis C have expanded in the previous two decades and the development of new agents has proven beneficial in patients who were previously resistant to interferon combination therapy, including those with genotypes 1 and 4.

Table 2. Summary of the Direct Acting Antiviral Agents*

Characteristic	Nucleoside polymerase inhibitors	Non-nucleoside polymerase inhibitors	NS5A inhibitors	Protease inhibitors
Potency	Moderate-to-high across all HCV genotypes	Varies by HCV genotype	High against multiple HCV genotypes	Varies by HCV genotype
Barrier to resistance	High	Very low	Low	Low
Potential for drug interactions	Low	Variable	Low-to-moderate	High
Toxicity	Mitochondrial toxicity	Variable	Variable	Rash, anemia, increased bilirubin
Dosing	2-3 times daily	1-3 times daily	1 time daily	1-3 times daily

*Adapted from Schaefer EA, Chung RT. Anti-hepatitis C virus drugs in development. Gastroenterology 2012; 142:1340[7]

The addition of a direct-acting HCV antiviral agent, like a protease inhibitor or nucleotide analogue inhibitor, to interferon/ribavirin therapy has demonstrated significantly increased treatment responses in patients with HCV genotype 1 infection, severe liver disease, cirrhosis, HIV co-infection and hepatocellular carcinoma. Table 2 provides a summary of the new direct-acting antiviral agents. Clinical trials demonstrate that the addition of these new medications to standard therapy provides SVR in up to 95% of previously treatment-resistant patients and the incidence of relapse is extremely low (<1%). In many instances, the new protease and nucleotide analogue inhibitor agents are recommended as first-line therapy options over the use of combination pegylated interferon and ribavirin. See Table 3 for a summary of the current guideline recommendations for treatment of Hepatitis C infections.[8,9]

Ledipasvir/sofosbuvir (Harvoni®) and ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®) are the two newest combination agents approved for use in the treatment of HCV (in October and December 2014).[4,5] Harvoni® and Viekira Pak® are indicated in the initial treatment or retreatment of HCV genotype 1 infection. Current practice guidelines also recommend Harvoni® and Viekira Pak® as first line treatment options in the initial treatment or retreatment of HCV genotype 4 infection and Harvoni® in the treatment of HCV genotype 6 infection. The combination agents have demonstrated efficacy when used for shorter treatment durations (12 weeks) compared to standard treatment durations (24-48 weeks) and are said to be associated with fewer adverse effects.[1-3] Clinical guideline recommendations for the treatment of hepatitis C are constantly changing due to the release of new therapies and changes in resistance patterns. Careful attention should be paid to current treatment recommendations and patient specific characteristics when initiating and selecting a hepatitis C therapy.

Table 3. Most Current Clinical Practice Guidelines for the Treatment of Hepatitis C Virus

Guideline	Recommendations
Recommendations for Testing, Managing, and Treating Hepatitis C by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA); as of June 28th, 2015[8]	Genotype 1 Initial treatment or Retreatment: LED/SOF x 12 weeks PAR/RIT/OMB + DAS ± RBV x 12-24 weeks SOF + SMV ± RBV x 12-24 weeks Alternatives in patients requiring retreatment: LED/SOF ± RBV x 12-24 weeks *Deferral of retreatment may be recommended in patients with minimal liver disease Genotype 2 Initial treatment or Retreatment: SOF + RBV x 12-16 weeks Alternatives in patients requiring retreatment: SOF + PEG/RBV x 12 weeks Genotype 3 Initial treatment or Retreatment: SOF + RBV ± PEG x 12-24 weeks Alternatives in patients requiring retreatment: SOF + PEG/RBV x 12 weeks Genotype 4 Initial treatment or Retreatment: LED/SOF x 12 weeks PAR/RIT/OMB + RBV x 12 weeks SOF + RBV ± PEG x 12-24 weeks SOF + SMV ± RBV x 12 weeks Alternatives: SOF + RBV x 24 weeks Genotype 5 Initial treatment or Retreatment: LED/SOF x 12 weeks SOF + PEG/RBV x 12 weeks Genotype 6 Initial treatment or Retreatment: LED/SOF x 12 weeks SOF + PEG/RBV x 12 weeks *The longer durations of therapy are recommended in patients with cirrhosis

Guidelines for the screening, care and treatment of persons with hepatitis C infection by the World Health Organization (WHO); 2014[9]	Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection. Treatment with telaprevir or boceprevir, given in combination with pegylated interferon and ribavirin, is suggested for genotype 1 chronic hepatitis C infection. Sofosbuvir, given in combination with ribavirin with or without pegylated interferon is recommended in genotypes 1, 2, 3 and 4 HCV infections. Simeprevir, given in combination with pegylated interferon and ribavirin, is recommended for persons with HCV genotype 1b infection and for persons with HCV genotype 1a infection without the Q80K polymorphism.

Key: PEG- Peginterferon, RBV- Ribavirin, SMV-Simeprevir, SOF- Sofosbuvir, LED- Ledipasvir, PAR/RIT/OMB- Ombitasvir/Paritaprevir/Ritonavir, DAS- Dasabuvir

Pharmacology

Interferons bind to the surface of cells infected with virus which results in activation of interferon-stimulated genes (ISGs) in the cell and inhibition of virus replication.[1-3] Ribavirin inhibits virus RNA polymerase activity and results in inhibition of viral protein synthesis. The new direct-acting antiviral agents demonstrate activity specifically in the hepatitis C virus. See Table 4 for a review of the pharmacokinetic properties associated with the different antiviral agents. Boceprevir, paritaprevir, simeprevir and telaprevir are referred to as protease inhibitors and the agents work by inhibiting a specific protease (NS3/4A) involved in HCV replication. Dasabuvir, ledipasvir, ombitasvir and sofosbuvir are polymerase inhibitors which inhibit key enzymes (NS5A or NS5B) responsible for HCV RNA synthesis.[10] Ledipasvir/sofosbuvir (Harvoni®) and ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®) are the two newest combination agents approved for use in the treatment of HCV.

Harvoni® combines 2 direct-acting hepatitis C polymerase inhibitors: ledipasvir, which inhibits the HCV NS5A protein required for viral replication, and sofosbuvir, which inhibits the NS5B RNA-dependent RNA polymerase also necessary for viral replication and acts as a chain terminator. Sofosbuvir is a pro-drug that is metabolized in the liver to its active form and inactive metabolites which are excreted mainly in the kidneys and may require dose reductions in patients with renal impairment. The rate of absorption of sofosbuvir is rapid and increases with increasing dose. Ledipasvir undergoes slow oxidative metabolism, does not exert any inhibitory cytochrome effects and, currently, no dose adjustments are required for Harvoni® therapy in patients with impaired hepatic function.[4,5,11]

Viekira Pak® is a fixed-dose combination tablet with ombitasvir, paritaprevir, and ritonavir along with an individual tablet of dasabuvir.[4,5] Each agent in the Viekira Pak® has a distinct mechanism of action: ombitasvir inhibits HCV NS5A, viral RNA replication and virion assembly; paritaprevir inhibits HCV NS3/4A protease, HCV coded polyprotein cleavage and viral replication; dasabuvir inhibits HCV RNA-dependent RNA polymerase (NS5B) and viral replication; and ritonavir is not active against HCV but is used to increase paritaprevir plasma drug concentrations. The absorption of each of the agents is not affected by food; however, the combination tablet should be taken with a meal to avoid gastrointestinal upset associated with ritonavir therapy. Ombitasvir is metabolized by amide hydrolysis, dasabuvir is metabolized by CYP2C8 and paritaprevir/ritonavir are metabolized by CYP3A. Ritonavir inhibits the CYP3A enzyme, effectively increasing both the peak and trough plasma drug concentrations of paritaprevir as well as overall drug exposure (by increasing AUC). Viekira Pak is not recommended for use in patients with moderate to severe hepatic impairment. Currently, no dose adjustments are recommended for Viekira Pak use in patients with renal impairment.

Table 4. Pharmacokinetics of the Hepatitis C Agents[4,5]

Agents	Route of Administration	Absorption	Distribution	Metabolism	Elimination
Interferon					
Peginterferon alfa-2a	Subcutaneous	T_{max}: 80-92 hours Bioavailability: 84%	Predominately bloodstream and extracellular fluid V_{ss}: 6 – 14 L	Unknown	Terminal $t_{1/2}$: 50-160 hours; increased with renal dysfunction
Peginterferon alfa-2b	Subcutaneous	$t_{1/2}$: 4.6 hours C_{max}: 2.5-4.4 ng/mL T_{max}: 15-44 hours Bioavailability: Increases with chronic dosing	Bloodstream and extracellular fluid	Unknown	Terminal $t_{1/2}$: 22-60 hours Renal (30%)
Nucleoside					
Ribavirin	Inhalation powder; Oral Capsule, Solution, Tablet	T_{max}: 2-3 hours Bioavailability: 64%	Prolonged in the erythrocyte (16-40 days) V_d: 2825 L	Hepatically and intracellularly (forms active metabolites)	Terminal $t_{1/2}$: 24-298 hours Urine (61%) Feces (12%)
Protease Inhibitor					
Boceprevir	Oral Capsule	T_{max}: 2 hours Food enhances absorption by up to 65%	V_d: ~772 L Protein binding: ~75%	Hepatic via aldo-ketoreductase or CYP 3A4/5 to inactive metabolites	Terminal $t_{1/2}$: ~3.4 hours Feces (79%) Urine (9%)
Simeprevir	Oral Capsule	T_{max}: 4-6 hours Food enhances absorption	Protein binding: >99% (albumin and alpha 1-acid glycoprotein)	Hepatic via CYP3A4, CYP2C8 and CYP2C19 to unchanged drug and metabolites (minor)	Terminal $t_{1/2}$: 10-13 hours (healthy volunteers); 41 hours (hepatitis C–infected patients) Feces (~91%) Urine (< 1%)
Telaprevir	Oral Tablet	T_{max}: 4-5 hours Food enhances absorption	V_d: ~252 L Protein binding: 59% to 76%	Hepatic to less active (30x) and inactive metabolites	Terminal $t_{1/2}$: ~9-11 hours Feces (82%) Urine (1%)
Polymerase Inhibitor					
Sofosbuvir	Oral tablet	T_{max}: ~0.5 to 2 hours	Protein binding: ~61% to 65%	Hepatic to active and inactive metabolites	Terminal $t_{1/2}$: 0.4 hours Urine (80%)

Agents	Route of Administration	Absorption	Distribution	Metabolism	Elimination
Combination Agents					
Ledipasvir and Sofosbuvir (Harvoni®)	One oral combination tablet	T_{max}: Ledipasvir: 4 to 4.5 hours; Sofosbuvir: ~0.8 to 1 hour $t_{1/2}$: Ledipasvir: 47 hours Sofosbuvir: ~0.5 hours	Protein binding: Ledipasvir: >99.8%; Sofosbuvir: 61% to 65%	Ledipasvir: Slow oxidative metabolism via an unknown mechanism Sofosbuvir: Hepatic; forms pharmacologically active nucleoside (uridine) analog triphosphate GS-461203; Dephosphorylation results in the formation of nucleoside inactive metabolite GS-331007	Ledipasvir: Feces (~86%), urine (1%) Sofosbuvir: Urine (80%), feces (14%)
Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir (Viekira Pak®)	One oral combination tablet (ombitasvir, paritaprevir, ritonavir) & One oral single agent (dasabuvir)	Bioavailability: Dasabuvir: ~70% T_{max}: 4-5 hours $t_{1/2}$: Ombitasvir: 21 to 25 hours; Paritaprevir: 5.5 hours; Ritonavir: 4 hours; Dasabuvir 5.5 to 6 hours	Ombitasvir: V_d: 50.1 L Paritaprevir: V_d: 16.7 L Ritonavir: V_d: 21.5 L Dasabuvir: V_d: 396 L Protein binding: Ombitasvir: 99.9%; Paritaprevir: ~98%; Ritonavir: >99%; Dasabuvir: >99%	Ombitasvir: amide hydrolysis and oxidative metabolism Paritaprevir: CYP3A4 and to a lesser extent CYP3A5 Ritonavir: CYP3A and to a lesser extent CYP2D6 Dasabuvir: CYP2C8 and to a lesser extent CYP3A	Ombitasvir: Feces (~90%, mainly as unchanged drug) and urine (<2%, mainly as unchanged drug) Paritaprevir: Feces (~88%, mainly as metabolites) and urine (~9%, mainly as metabolites) Ritonavir: Feces (~86%) and urine (~11%) Dasabuvir: Feces (~94%, mainly as metabolites) and urine (~2%, mainly as metabolites)

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2015), the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE, evaluating efficacy of the new combination agents in the treatment of Hepatitis C Virus are included. Trials evaluating the new hepatitis agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded.[11-15]

Clinical Efficacy

Harvoni. Seven clinical trials evaluating the efficacy of the sofosbuvir/ledipasvir combination agent are available for evaluation. The available trials evaluated sofosbuvir/ledipasvir alone or in combination with ribavirin in patients with hepatitis C genotype 1 infection. In addition, a number of clinical trials evaluating the single agents sofosbuvir and ledipasvir are available for evaluation. The Evidence Table in the appendix provides a summary of the available trials.

In 2014, Gane et al[16] published results from the ongoing ELECTRON clinical trial. In this arm of the study, 113 patients with HCV genotype 1 received sofosbuvir and ledipasvir with ribavirin for 6-12 weeks or sofosbuvir and the NS5B non-nucleoside inhibitor GS-9669 with ribavirin for 12 weeks. At 12 weeks, SVR rates were 100% in patients receiving sofosbuvir and ledipasvir with ribavirin for 12 weeks, 68% in patients receiving sofosbuvir and ledipasvir with ribavirin for 6 weeks and 92% in patients receiving sofosbuvir and the NS5B non-nucleoside inhibitor GS-9669 with ribavirin for 12 weeks. The authors also reported an SVR of 70% for patients who received sofosbuvir and ledipasvir without ribavirin for 12 weeks. The most common adverse events reported in the trial were headache, fatigue and nausea.

Three open-label, phase 3 trials evaluating ledipasvir/sofosbuvir combination therapy were published in 2014. Afdahl et al[17,18] published two of the trials. The first, a relatively large trial evaluating 865 patients, evaluated the efficacy of combination therapy in previously untreated patients with HCV genotype 1. Patients received ledipasvir/sofosbuvir for 12-24 weeks or ledipasvir/sofosbuvir plus ribavirin for 12-24 weeks. SVR rates at 12 weeks were 97-99% across all treatment groups and durations. The most common adverse events reported in the trial were fatigue, headache, insomnia and nausea. The second trial evaluated the efficacy of combination therapy in 440 treatment-resistant patients with HCV genotype 1. SVR rates at 12 weeks were 99% in patients receiving 24 weeks of ledipasvir/sofosbuvir with or without ribavirin therapy and 94-96% in patients receiving 12 weeks of ledipasvir/sofosbuvir with or without ribavirin therapy. The most common adverse events reported in this trial were fatigue, headache and nausea. Kowdley et al[19] published a trial evaluating 647 patients with HCV genotype

1 who received no previous treatment for HCV and who did not have evidence of cirrhosis. Patients received ledipasvir/sofosbuvir therapy for 8-12 weeks or ledipasvir/sofosbuvir plus ribavirin for 8 weeks. SVR rates at 12 weeks were 93-95% across all treatment groups and durations. The most common adverse events reported in the trial were fatigue, headache and nausea, with the highest rates of adverse events reported in the ribavirin treatment group.

Three small, open-label, phase 3 trials evaluating ledipasvir/sofosbuvir combination therapy were published in 2014-15. Osinusi et al[20,21] published two of the trials. The first evaluated the efficacy of the agents in 50 treatment-naïve patients with HCV genotype 1 and an HIV co-infection. Patients received ledipasvir/sofosbuvir combination therapy for 12 weeks. At the end of the study period, an SVR of 98% (49/50) was reported with the most frequent adverse events listed as nasal congestion (16%) and myalgia (14%). The second trial evaluated 14 treatment-resistant patients with HCV genotype 1. Patients received ledipasvir/sofosbuvir combination therapy for 12 weeks and had an SVR rate of 100% at the end of the study period. The most common adverse events reported in the trial were myalgia and hypophosphatemia. Kohli et al[22] evaluated the efficacy of ledipasvir and sofosbuvir in 60 previously untreated patients with HCV genotype 1. Patients received ledipasvir and sofosbuvir for 12 weeks or ledipasvir and sofosbuvir in combination with a third direct acting agent (GS-9669 or GS-9451) for 6 weeks. The SVR at 12 weeks was 100% (20/20) in the ledipasvir/sofosbuvir for 12 weeks treatment group and 95% (19/20) in the triple therapy for 6 weeks treatment group. The most common adverse events reported in the trial were diarrhea, headache and fatigue.

Viekira Pak. Six clinical trials evaluating the efficacy of ombitasvir, paritaprevir, ritonavir and dasabuvir combination therapy (OPRD), are available for evaluation. The available trials evaluated this combination therapy with or without concomitant ribavirin therapy in patients with hepatitis C genotype 1 infection. The Evidence Table in the appendix provides a summary of the available trials.

Two clinical trials evaluated the efficacy of ombitasvir, paritaprevir, ritonavir and dasabuvir combination therapy in treatment-naïve patients. Ferenci et al[23] evaluated the efficacy of OPRD in 724 patients with HCV genotype 1a or 1b infection who were previously untreated and did not have a diagnosis for cirrhosis. Patients received the combination therapy with or without ribavirin therapy for 12 weeks. The SVR rate at 12 weeks was 97.5-99% in the OPRD with ribavirin treatment group and 90.2-99% in the OPRD without ribavirin treatment group. Overall adverse event rate and decreases in hemoglobin level were reported more frequently in the ribavirin treatment group compared to the ribavirin-free treatment group ($p \leq 0.03$). The most common adverse events reported in the study were fatigue, headache and nausea. Feld et al[24] evaluated the efficacy of OPRD combination therapy in 631 previously untreated patients with HCV genotype 1 infection. Patients were randomized to receive either placebo or ORPD combination therapy with ribavirin for 12 weeks. At the end of the study period, SVR was 96.2% in the active treatment group. Overall adverse event rate was higher in the

active treatment group (87.5%) compared to the placebo group (73.4%; $p < 0.001$) and the most frequently reported adverse events were nausea, pruritis, insomnia, diarrhea and asthenia.

Two clinical trials evaluated the efficacy of ombitasvir, paritaprevir, ritonavir and dasabuvir combination therapy in treatment-resistant patients. Andreone at al[25] evaluated the efficacy of OPRD in 179 treatment-resistant patients with HCV genotype 1b without cirrhosis. Patients received the combination therapy with or without ribavirin therapy for 12 weeks. SVR results were compared to the SVR rates to those of a similar population treated with telaprevir, peginterferon and ribavirin. At the end of the treatment period, SVR rates were 96.6% in the OPRD with ribavirin treatment group and 100% in the OPRD without ribavirin treatment group compared to 64% in the historical comparator group. The most common adverse events reported in the trial were fatigue and headache. Decreases in hemoglobin level occurred more frequently in the ribavirin treatment group (42% vs 5.5%; $p < 0.001$). Zeuzem at al[26] evaluated the efficacy of OPRD in 394 patients with HCV genotype 1 infection and no cirrhosis, previously treated with peginterferon-ribavirin combination therapy. Patients were randomized to receive either placebo or ORPD combination therapy with ribavirin for 12 weeks. At the end of the study period, SVR was 96.3% in the active treatment group. Overall adverse event rate was 91.2% in the active treatment group and 82.5% in the placebo group (p = NS). The most frequently reported adverse events were headache and fatigue and pruritis was reported more frequently in the active treatment group (13.8%) compared to the placebo group (5.2%; $p = 0.03$).

Two clinical trials evaluated the efficacy of ombitasvir, paritaprevir, ritonavir and dasabuvir combination therapy in mixed populations of treatment- naïve and treatment-resistant patients. Poordad et al[27] evaluated the efficacy of OPRD in combination with ribavirin in 380 previously untreated and previously treated adult patients with HCV genotype 1 infection and compensated cirrhosis. Patients who received the combination therapy for 12 weeks had an SVR rate of 91.8% and patients who received combination therapy for 24 weeks had an SVR rate of 95.9%. The most common adverse events reported in the study were fatigue, headache and nausea. Kowdley et al[28] evaluated the efficacy of combination therapy in 571 patients with HCV genotype 1 infection without cirrhosis who had not received treatment previously or who had not had a favorable response to prior therapy. Patients received ombitasvir, paritaprevir, ritonavir and dasabuvir in combination with ribavirin (V+R) OR ombitasvir, paritaprevir, ritonavir in combination with ribavirin OR dasabuvir, paritaprevir, ritonavir in combination with ribavirin for 8, 12 or 24 weeks. SVR rates across all treatment groups ranged from 83-100% and the most frequently reported adverse events in the trial were fatigue, headache, nausea and insomnia.

Special Populations

Despite continued advances in pharmacologic treatment options for HCV, risk factors still exist which are associated with poor treatment outcomes, including black

race, advanced liver fibrosis, cirrhosis, HCV genotypes 1 and 4, high baseline HCV viral loads and other genetic mutations.[1,2] In these patient populations, the direct acting protease inhibitors and polymerase inhibitors may be used in combination to improve sustained viral responses. Many trials have evaluated the combined use of the agents in patients with genotype 1 and advanced disease and/or previous treatment-resistance and have reported increased rates of efficacy with similar or reduced rates of adverse events with the direct acting antiviral agents compared to ribavirin/interferon therapy. Ombitasvir, paritaprevir, ritonavir and dasabuvir combination therapy was also evaluated in patients co-infected with HIV as well as patients who have received a liver transplant.

In 2015, Sulkowski et al[29] published a trial evaluating 63 patients with HCV and co-infected with HIV who were at high risk for liver disease progression. Patients received combination therapy with ombitasvir, paritaprevir, ritonavir and dasabuvir for 12-24 weeks. SVR rates were reported as 94% (29/31) in the patients who received 12 weeks of therapy and 91% (29/32) in patients who received 24 weeks of therapy. Of the 5 patients who did not achieve an SVR: one withdrew consent, two had clinical history and phylogenetic evidence consistent with HCV reinfection and two had confirmed virologic relapse or breakthrough. The most common treatment-emergent adverse events reported in the trial were fatigue (48%), insomnia (19%), nausea (18%) and headache (16%). In 2014, Kwo et al[30] published a trial evaluating 34 liver-transplant recipients with recurrent HCV genotype 1 infection. Patients received combination therapy with ombitasvir, paritaprevir, ritonavir and dasabuvir for 24 weeks. At the end of the study period, SVR was reported as 97% (33/34) and the most common adverse events reported in the trial were fatigue, headache and cough.

Adverse Drug Reactions

The newer HCV therapeutic agents allow for shorter treatment regimens and easier to tolerate treatment courses with similar or increased rates of efficacy. In addition, the move to interferon-free treatment regimens eliminates the need for subcutaneous injections, improves medication adherence rates and reduces the incidence of influenza-like symptoms, fever, depression and hematologic events.[1-3,6] Table 5 provides a list of serious drug-drug interactions reported with the new HCV agents and Table 6 provides a summary of the adverse events associated with the HCV therapeutic options, based on package labeling.

The first generation protease inhibitors, telaprevir and boceprevir, were approved for use in 2011 for the treatment of hepatitis C genotype 1 infections in combination with standard therapy of peginterferon and ribavirin. These first generation agents are given two to three times a day and have demonstrated increased rates of adverse effects compared to standard therapy. Adverse effects associated with telaprevir therapy included anemia, rash and perianal itching. Adverse effects associated with boceprevir included anemia and dysgeusia.[31] Paritaprevir and simeprevir are considered second-generation protease inhibitors, are dosed once daily and are associated with fewer adverse events compared to the first-generation agents. The most common adverse events reported with the second-generation agents include rash, photosensitivity, pruritus and nausea. More serious adverse events associated with the protease inhibitors include increased serum bilirubin and use is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B or C). Paritaprevir and simeprevir are metabolized in the liver by CYP3A4 and should be used with caution when given with other medications which inhibit or induce the CYP3A4 enzyme.[4,5]

The HCV NS5A inhibitors, ledipasvir and ombitasvir, are a new group of potent direct-acting antiviral agents with efficacy across all genotypes. As a class, the agents tend to have a low barrier to resistance and variable toxicity profiles.[32] The NS5A inhibitors are currently only available in fixed-dose combinations with other direct-acting antiviral agents. The most common adverse events reported in clinical trials evaluating the safety and efficacy of sofosbuvir-ledipasvir combination therapy and ombitasvir combination therapy include fatigue, headache, nausea and insomnia.[4,5] Daclatasvir is an NS5A inhibitor in the late stage of development in the United States and available for use in Europe and Japan. Elbasvir is another NS5A inhibitor used in combination with the protease inhibitor grazoprevir, currently under development in the US.

The polymerase inhibitors, sofosbuvir and dasabuvir, are a third class of direct-acting antiviral agents used in the treatment of HCV.[32] As a single agent, treatment with sofosbuvir is well tolerated and demonstrates reduced rates of treatment discontinuation and few adverse events.[33] It appears the most common adverse events reported with sofosbuvir use include central nervous system events (headache, fatigue, insomnia) and gastrointestinal events (nausea and decreased appetite).[4,5] Hepatic and hematologic adverse events are not reported with sofosbuvir use. In March 2015, the FDA approved labeling changes to Harvoni® and sofosbuvir to warn of serious and life-threatening

cases of symptomatic bradycardia when used in combination with amiodarone and concurrent administration is not recommended. Currently, dasabuvir is only available in fixed-dose combinations with ombitasvir, paritaprevir and ritonavir and the most frequent adverse events reported in clinical trials evaluating the combination therapy include headache, nausea and insomnia. Overall, sofosbuvir and dasabuvir appear to have favorable safety and tolerability profiles. Unlike dasabuvir, sofosbuvir is excreted mainly in the kidneys and may require dose reductions in patients with renal impairment. [4,5]

Table 5. Serious Drug-Drug Interactions Reported with the New HCV Agents[4,5]

Harvoni®	
Antiarrhythmic agents	Sofosbuvir may enhance the bradycardic effect of Amiodarone and other antiarrhythmic agents
Bosutinib, Pazopanib, Rosuvastatin, Silodosin, Topotecan, Vincristine	P-glycoprotein/ABCB1 Inhibitors, like ledipasvir, may increase the serum concentration of Bosutinib, Pazopanib, Rosuvastatin, Silodosin, Topotecan, Vincristine
P-glycoprotein/ABCB1 Inducers	P-glycoprotein/ABCB1 Inducers (Carbamazepine; Dexamethasone; Doxorubicin; Fosphenytoin; Nefazodone; Phenobarbital; Phenytoin; Primidone; Rifampin; St Johns Wort; Tipranavir; Vinblastine) may decrease the serum concentration of Sofosbuvir
Modafinil	Modafinil may decrease the serum concentration of Sofosbuvir
Oxcarbazepine	Oxcarbazepine may decrease the serum concentration of Sofosbuvir
Rifabutin	Rifabutin may decrease the serum concentration of Sofosbuvir
Rifapentine	Rifapentine may decrease the serum concentration of Sofosbuvir
Simeprevir	Simeprevir may increase the serum concentration of Ledipasvir
Viekira Pak®	
Bosutinib, Pazopanib, Rosuvastatin, Silodosin, Topotecan, Vincristine	P-glycoprotein/ABCB1 Inhibitors, like ledipasvir, may increase the serum concentration of Bosutinib, Pazopanib, Rosuvastatin, Silodosin, Topotecan, Vincristine
CYP3A4 substrates	Strong CYP3A4 Inhibitors (like Ritonavir) may increase serum concentrations of the active metabolite(s) of CYP3A4 substrates (Ado-Trastuzumab Emtansine, Alfuzosin, Amiodarone, Apixaban, Astemizole, Atovaquone, Axitinib, Cabozantinib, CarBAMazepine, Ceritinib, Conivaptan, Crizotinib, Dapoxetine, Domperidone, Dronedarone, Enzalutamide, Eplerenone, Etravirine, Everolimus, Flecainide, Fluticasone, Fosphenytoin, Fusidic Acid, Halofantrine, Ibrutinib, Idelalisib, Irinotecan, Lapatinib, Lercanidipine, Lomitapide, Lovastatin, Lurasidone, Mitotane, Naloxegol, Nilotinib, Nisoldipine, Olaparib, Phenobarbital, Palbociclib, Phenytoin, Primidone, Propafenone, Quinidine, Quinine, Ranolazine, Red Yeast Rice, Regorafenib, Rifabutin, Rivaroxaban, Salmeterol, Simeprevir, St Johns Wort, Suvorexant, Tamsulosin, Ticagrelor, Tolvaptan, Toremifene, Triazolam, Vemurafenib, Vorapaxar, Voriconazole)
Ergot Derivatives	Protease Inhibitors may increase the serum concentration of Ergot Derivatives (Bromocriptine; Dihydroergotamine; Ergoloid Mesylates; Ergonovine; Ergotamine; Methylergonovine)
Cisapride	Protease Inhibitors may increase the serum concentration of Cisapride. This may result in QTc prolongation and malignant cardiac arrhythmias.
Strong CYP2C8 Inhibitors	Strong CYP2C8 Inhibitors (like Clopidogrel; Gemfibrozil; Ritonavir; Stiripentol) may increase the serum concentration of Dasabuvir
Efavirenz	Efavirenz may enhance the adverse/toxic effect of Paritaprevir. Efavirenz may decrease the serum concentration of Paritaprevir.
Ethinyl Estradiol	Ethinyl Estradiol may enhance the hepatotoxic effect of Dasabuvir.
Mequitazine, Tamoxifen, Thioridazine	Strong CYP2D6 Inhibitors (like ritonavir) may increase the serum concentration of Mequitazine, Tamoxifen, Thioridazine
Midazolam	Protease Inhibitors may increase the serum concentration of Midazolam
Pimozide	Protease Inhibitors may increase the serum concentration of Pimozide
Rifampin	Rifampin may decrease the serum concentration of Ritonavir
Simvastatin	Protease Inhibitors may increase the serum concentration of Simvastatin

Table 6. Adverse Events Reported with the Hepatitis C Virus Therapeutic Agents[4,5]

	Boceprevir (%)	Harvoni® (%)	Peginterferon alfa (%)	Ribavirin (%)	Simeprevir (%)	Sofosbuvir (%)	Telaprevir (%)	Viekira Pak® (%)
Cardiovascular	--	Bradycardia and cardiac arrest (with amiodarone coadministration)	Chest pain (6) Flushing (6) Bundle branch block (4) Myocardial infarction (4) Supraventricular arrhythmia (4) Ventricular tachycardia (4)	Chest pain (5-9) Flushing (≤4)	--	--	--	--
Central Nervous System	Chills (33-34) Dizziness (16-19) Fatigue (55-58) Headache (>10)Insomnia (30-34) Irritability (21-22)	Fatigue (13-18) Headache (11-17) Insomnia (3-6)	Agitation (2) Anxiety/emotional liability/irritability (28) Chills (≤63) Concentration impaired (10) Depression (29-59) Dizziness (12-35) Fatigue (52-94) Fever (22-75) Headache (56-70) Insomnia (23) Malaise (7) Nervousness (4) Olfactory nerve disorder (≤23) Suicidal behavior (≤2)	Agitation (5-8) Anxiety (11) Depression (20-36) Dizziness (14-26) Emotional lability (7-12) Fatigue (60-70) Fever (32-55) Headache (43-66) Impaired concentration (10-21) Insomnia (26-41) Irritability (23-33) Malaise (≤6) Memory impairment (≤6) Mood alteration (≤6-9) Nervousness (6) Pain (≤13) Suicidal ideation (1-2)	--	Chills (2-17) Fatigue (30-59) Headache (24-36) Insomnia (15-25) Irritability (10-13) Severe depression (<1) Suicidal ideation (<1)	Fatigue (56)	Fatigue (34-50) Headache (16-44) Insomnia (5-26) Irritability (10)
Dermatologic	Alopecia (22-27) Angioedema (<1) DRESS syndrome (<1) Dry skin (18-22) Exfoliative dermatitis (<1) Exfoliative rash (<1) Mouth ulceration (<1) Rash (16-17) Stevens-Johnson syndrome (<1) Toxic skin eruption (<1)	--	Alopecia (22-34) Dry skin (11) Pruritus (12) Rash (6-36)	Alopecia (27-36) Dermatitis (≤16) Dry skin (10-24) Eczema (4-5) Pruritus (13-29) Rash (5-28)	Pruritus (22) Skin photosensitivity (1-5) Skin rash (28)	Pruritus (11-27) Skin rash (8-18)	DRESS syndrome (<1) Erythema multiforme (<1) Pruritus (47) Rash (56) Stevens-Johnson syndrome (<1) Toxic epidermal necrolysis (<1)	Dermatological reaction (7-24) Pruritus (7-18)
Metabolic	--	--	Hypothyroidism (5) Menstrual disorder	Growth suppression (25-43)	--	--	Hyperuricemia (7-66)	--

			(4)	Hyperuricemia (33-38) Hypothyroidism (≤5) Menstrual disorder (≤7)				
Gastrointestinal	Abnormal taste (35-44) Appetite decreased (25-26) Diarrhea (24-25) Nausea (43-46) Vomiting (15-20) Xerostomia (11-15)	Nausea (6-9) Diarrhea (3-7) Increased serum lipase (>3 x ULN: ≤3)	Abdominal pain (8-15) Anorexia (20-69) Constipation (1) Diarrhea (18-37) Dyspepsia (6) Nausea (26-64) Taste perversion (≤38) Vomiting (7-26) Weight loss (11) Xerostomia (6)	Abdominal pain (8-13) Anorexia (21-32) Constipation (5) Diarrhea (10-22) Dyspepsia (6-16) Nausea (25-47) Right Upper Quadrant pain (≤12) Taste perversion (≤9) Vomiting (9-25) Weight decrease (10-29) Xerostomia (≤12)	Nausea (22)	Decreased appetite (18) Diarrhea (9-12) Increased serum lipase (≤2%) Nausea (22-34)	Abnormal taste (10) Anal pruritus (6) Anorectal discomfort (11) Diarrhea (26) Hemorrhoids (12) Nausea (39) Vomiting (13)	Diarrhea (26) Nausea (8-24)
Hematologic	Agranulocytosis (<1) Anemia (45-50) Neutropenia (14-31) Pancytopenia (<1) Thrombocytopenia (1-10) Urticaria (<1)	--	Anemia (6-47) Neutropenia (6-70) Thrombocytopenia (7-20)	Anemia (11-17) Hemoglobin decreased (11-35) Hemolytic anemia (10-13) Leukopenia (6-45) Lymphopenia (12-14) Neutropenia (8-42) Thrombocytopenia (<1-15)	--	Pancytopenia (<1) Thrombocytopenia (≤1)	Anemia (36) Lymphopenia (15) Thrombocytopenia (3)	Decreased hemoglobin (<1-29)
Hepatic	--	Hyper-bilirubinemia (>1.5 x ULN: ≤3)	Alkaline phosphatase increased (≤23) ALT/AST increased (10-77) GGT increased (8) Hepatomegaly (6)	Bilirubin increase (10-32) Hepatic decompensation (2) Hepatomegaly (4) Transaminases increased (1-3)	Increased serum alkaline phosphatase (<4) Increased serum bilirubin (<50)	Decreased hemoglobin (6-23) Decreased neutrophils (5-15) Increased serum bilirubin (3) Neutropenia (<1-17)	--	Increased serum bilirubin (2-54) Increased serum ALT (1-25)
Neuromuscular & skeletal	Arthralgia (19-23) Weakness (15-21)	--	Arthralgia (23-51) Musculoskeletal pain (28) Myalgia (54-68) Paresthesia (21) Rigors (23) Weakness (52)	Arthralgia (21-34) Back pain (5) Decreased linear skeletal growth (70) Musculoskeletal pain (19-35) Myalgia (40-64) Rigors (25-48) Weakness (9-10)	Myalgia (16)	Myalgia (6-14) Weakness (5-21)	--	Weakness (4-24) Muscle spasm (21)
Ophthalmic	--	--	Blurred vision (2) Conjunctivitis (4)	Blurred vision (≤6) Conjunctivitis (≤5)	--	--	--	Scleral icterus (10)
Renal	--	--	Proteinuria (≤7)	--	--	Increased creatine kinase (1-2)	Prerenal azotemia (<1) Uric acid nephropathy (<1)	--
Respiratory	Dyspnea (8-11)	--	Cough (5-8) Dyspnea (4-6)	Cough (7-23) Dyspnea (13-26)	Dyspnea (12)	--	--	Cough (11-32) Dyspnea

			Pharyngitis (10) Rhinitis (2) Sinusitis (7)	Exertional dyspnea (≤7) Pharyngitis (≤13) Rhinitis (≤8) Sinusitis (≤12) Upper respiratory tract infection (60)				
Miscellaneous	Pneumonia (<1) Sepsis (<1)	--	Binding antibodies (35) Diaphoresis (6) Injection site reaction (23-62) Neutralizing antibodies (≤2) Viral infection (11)	Bacterial infection (3-5) Diaphoresis (≤11) Flu-like syndrome (13-91) Fungal infection (≤6) Injection site reaction (36-58) Viral infection (≤12)	--	Fever (4-18) Flu-like symptoms (6-16)	--	--

Summary

Treatment of hepatitis C virus is extensive and requires long-term (up to 48 weeks) treatment with two to five agents. Currently, nine agents available for the treatment of HCV including: boceprevir, Harvoni®, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, simeprevir, sofosbuvir, telaprevir and Viekira Pak®. The standard of care for the treatment of HCV varies depending on virus genotype and individual patient characteristics. Treatment options available for chronic hepatitis C have expanded in the previous two decades and the development of new agents has proven beneficial in patients who were previously resistant to interferon combination therapy, including those with genotype 1. Ledipasvir/sofosbuvir (Harvoni®) and ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®), the two newest combination agents approved for use in the treatment of HCV, are indicated in the initial treatment or retreatment of HCV genotype 1 infection. Current practice guidelines also recommend Harvoni® and Viekira Pak® as first line treatment options in the treatment of HCV genotype 4 infection and Harvoni® in the treatment of HCV genotype 6 infection. These combination agents appear to be the most effective, with sustained virologic responsiveness (SVR), in patients with HCV genotypes 1and 4.

Seven clinical trials evaluating the efficacy of ledipasvir/sofosbuvir combination therapy and six clinical trials evaluating the efficacy of ombitasvir/paritaprevir/ritonavir/dasabuvir combination therapy are available for evaluation. Overall, the evidence suggests these combination therapies demonstrate efficacy in the treatment of hepatitis C genotypes 1 and produce sustained virologic response rates of ~80-100%. Based on the clinical evidence, interferon-free regimens produce similar rates of efficacy without the need for subcutaneous injections and with reduced rates of adverse events (including influenza-like symptoms, fever, depression and hematologic events). In addition to improving rates of efficacy, the newer HCV therapeutic agents allow for shorter treatment durations and easier to tolerate treatment courses. Overall, Harvoni® and Viekira Pak® are well-tolerated. The most common adverse events reported in clinical trials include fatigue, headache, insomnia and nausea.

The decision to treat a patient with HCV is a complicated one which requires careful consideration of when to initiate treatment, how long to treat the patient and which therapeutic agents to use. The decision to initiate treatment is based on severity of disease and presence or absence of various laboratory markers. The decision for duration of treatment is based on the hepatitis C genotype and other comorbidities present. The decision on which agents should be used is based on patient history and current medication regimen in addition to all of the previous factors. The risks and benefits of therapy should be considered before initiating any treatment.

References

1. Dienstag JL. Chapter 306. Chronic Hepatitis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012.
2. Dienstag JL. Chapter 304. Acute Viral Hepatitis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012.
3. Ryan KJ, Ray C. Chapter 13. Hepatitis Viruses. . In: Ryan KJ, Ray C, eds. *Sherris Medical Microbiology*. 5th ed. New York, NY: McGraw-Hill; 2010.
4. McEvoy GK, Snow EK, Kester L, Litvak K, Miller J, Welsh OH, eds. *AHFS 2014 Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2014.
5. Lexi-Comp I, ed *Drug Information Handbook.* 21st ed. Hudson, OH: Lexi-Comp; 2014.
6. Hepatitis C. In: National Center for HIV/AIDS VH, STD, and TB Prevention, ed: CDC; 2014.
7. Schaefer EA, Chung RT. Anti-hepatitis C virus drugs in development. *Gastroenterology.* May 2012;142(6):1340-1350 e1341.
8. AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. 2014.
9. Organization WH. Guidelines for the screening, care and treatment of persons with hepatitis C infection. 2014.
10. de Kanter CT, Drenth JP, Arends JE, et al. Viral hepatitis C therapy: pharmacokinetic and pharmacodynamic considerations. *Clinical pharmacokinetics.* May 2014;53(5):409-427.
11. Gentile I, Buonomo AR, Borgia F, Castaldo G, Borgia G. Ledipasvir : a novel synthetic antiviral for the treatment of HCV infection. *Expert opinion on investigational drugs.* Apr 2014;23(4):561-571.
12. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *The Lancet infectious diseases.* May 2013;13(5):401-408.
13. Yoshida EM, Sulkowski MS, Gane EJ, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. *Hepatology (Baltimore, Md.).* Jan 2015;61(1):41-45.
14. Yang H, Robinson M, Corsa AC, et al. Preclinical characterization of the novel hepatitis C virus NS3 protease inhibitor GS-9451. *Antimicrob Agents Chemother.* 2014;58(2):647-653.
15. Lawitz EJ, Gruener D, Hill JM, et al. A phase 1, randomized, placebo-controlled, 3-day, dose-ranging study of GS-5885, an NS5A inhibitor, in patients with genotype 1 hepatitis C. *Journal of hepatology.* Jul 2012;57(1):24-31.
16. Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. *Gastroenterology.* Mar 2014;146(3):736-743.e731.
17. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *The New England journal of medicine.* Apr 17 2014;370(16):1483-1493.
18. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *The New England journal of medicine.* May 15 2014;370(20):1889-1898.
19. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *The New England journal of medicine.* May 15 2014;370(20):1879-1888.
20. Osinusi A, Kohli A, Marti MM, et al. Re-treatment of chronic hepatitis C virus genotype 1 infection after relapse: an open-label pilot study. *Annals of internal medicine.* Nov 4 2014;161(9):634-638.
21. Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA : the journal of the American Medical Association.* Mar 24-31 2015;313(12):1232-1239.
22. Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. *Lancet.* Mar 21 2015;385(9973):1107-1113.
23. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *The New England journal of medicine.* May 22 2014;370(21):1983-1992.
24. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *The New England journal of medicine.* Apr 24 2014;370(17):1594-1603.

25. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology.* Aug 2014;147(2):359-365.e351.
26. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *The New England journal of medicine.* Apr 24 2014;370(17):1604-1614.
27. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *The New England journal of medicine.* May 22 2014;370(21):1973-1982.
28. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *The New England journal of medicine.* Jan 16 2014;370(3):222-232.
29. Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA : the journal of the American Medical Association.* Mar 24-31 2015;313(12):1223-1231.
30. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *The New England journal of medicine.* Dec 18 2014;371(25):2375-2382.
31. Feeney ER, Chung RT. Antiviral treatment of hepatitis C. *Bmj.* 2014;348:g3308.
32. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. *Lancet.* Mar 21 2015;385(9973):1124-1135.
33. Rose L, Bias TE, Mathias CB, Trooskin SB, Fong JJ. Sofosbuvir: A Nucleotide NS5B Inhibitor for the Treatment of Chronic Hepatitis C Infection. *The Annals of pharmacotherapy.* May 8 2014;48(8):1019-1029.
34. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *JAMA : the journal of the American Medical Association.* Aug 28 2013;310(8):804-811.
35. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet.* Jun 15 2013;381(9883):2100-2107.
36. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *The New England journal of medicine.* May 16 2013;368(20):1878-1887.
37. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *The New England journal of medicine.* May 16 2013;368(20):1867-1877.
38. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *The New England journal of medicine.* May 22 2014;370(21):1993-2001.
39. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet.* Jul 26 2014.
40. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *The New England journal of medicine.* Jan 3 2013;368(1):34-44.
41. Molina JM, Orkin C, Iser DM, et al. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. *Lancet.* Mar 21 2015;385(9973):1098-1106.

Appendix: Evidence Tables

Evidence Table 1. Clinical Trials Evaluating Ledipasvir and Sofosbuvir

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Osinusi et al, 2015[34] Open-label, single-center, phase 2b pilot study	50	Previously untreated, noncirrhotic patients with HCV genotype 1 and HIV co-infection	Ledipasvir (90 mg) and Sofosbuvir (400 mg) combination tablet once daily Duration: 12 weeks; conducted June 2013 to September 2014	Sustained Viral Response at 12 weeks: 49/50 participants (98% [95% CI, 89% to 100%])	Most common adverse events: nasal congestion (16% of patients) and myalgia (14%)
Kohli et al, 2015[22] Single-centre, open-label, phase 2A trial	60	Treatment-naïve patients with HCV genotype 1 infection	Sofosbuvir and Ledipasvir x 12 weeks Sofosbuvir, Ledipasvir, GS-9669 x 6 weeks Sofosbuvir, Ledipasvir, GS-9451 x 6 weeks Duration: 6-12 weeks	Sustained Viral Response at 12 weeks: • Sof/Led x12w: 20/20 (100%, 95% CI 83-100) • Sof/Led/GS-9669 x6w: 19/20 (95%, 75-100) • Sof/Led/GS-9451 x6w: 19/20 (95%, 75-100)	The most common adverse events: diarrhea, headache, fatigue
Osinusi et al, 2014[34] Phase 2a, open-label study	14	Patients with HCV GT-1 that relapsed after treatment with sofosbuvir plus ribavirin for 24 weeks	Sofosbuvir plus ledipasvir Duration: 12 weeks	Sustained Viral Response at 12 weeks: 100%	The most common adverse events were myalgia and hypophosphatemia
Afdahl etal, 2014[18] Phase 3, open-label study	865	Previously untreated patients with chronic HCV genotype 1 infection	Ledipasvir/sofosbuvir (L/S) once daily x 12 weeks Ledipasvir/sofosbuvir plus ribavirin (L/S+R) once daily x 12 weeks Ledipasvir/sofosbuvir once daily x 24 weeks Ledipasvir-sofosbuvir plus ribavirin once daily x 24 weeks	Sustained Viral Response at 12 weeks: • L/Sx12: 99% (95% CI, 96 to 100) • L/S+Rx12: 97% (95% CI, 94 to 99) • L/Sx24: 98% (95% CI, 95 to 99) • L/S+Rx24: 99% (95% CI, 97 to 100)	The most common adverse events: fatigue, headache, insomnia, nausea

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Afdahl etal, 2014[17] Phase 3, randomized, open-label study	440	Patients infected with HCV genotype 1 who had not had a sustained virologic response after treatment with peginterferon and ribavirin, with or without a protease inhibitor	Ledipasvir/sofosbuvir (L/S) once daily x 12 weeks Ledipasvir/sofosbuvir plus ribavirin (L/S+R) once daily x 12 weeks Ledipasvir/sofosbuvir once daily x 24 weeks Ledipasvir-sofosbuvir plus ribavirin once daily x 24 weeks	Sustained Viral Response at 12 weeks: • L/Sx12: 94% (95% CI, 87-97) • L/S+Rx12: 96% (95% CI, 91-99) • L/Sx24: 99% (95% CI, 95-100) • L/S+Rx24: 99% (95% CI, 95-100)	The most common adverse events: fatigue, headache, nausea
Kowdley et al, 2014[19] Phase 3, open-label study	647	Previously untreated patients with HCV genotype 1 infection without cirrhosis	Ledipasvir/sofosbuvir (L/S) x 8 weeks Ledipasvir/sofosbuvir plus ribavirin (L/S+R) x 8 weeks Ledipasvir/sofosbuvir x 12 weeks	Sustained Viral Response at 12 weeks: • L/Sx12: 94% (95% CI, 90-97) • L/S+Rx12: 93% (95% CI, 89-96) • L/Sx24: 95% (95% CI, 92-98)	The most common adverse events: fatigue, headache, nausea Adverse event rate: L/S+R > L/S
Gane et al, 2014; ELECTRON[16] Phase II, open-label, randomized trial	113	Patients with genotype 1 hepatitis C virus (HCV) infection.	Sofosbuvir 400 mg once daily and Ledipasvir 90 mg once daily plus ribavirin x 12 weeks Sofosbuvir 400 mg once daily and GS-9669 500 mg once daily plus ribavirin x 12 weeks Sofosbuvir 400 mg once daily and Ledipasvir 90 mg once daily plus ribavirin x 6 weeks Sofosbuvir 400 mg once daily and Ledipasvir 90 mg once daily without ribavirin x 12 weeks	Sustained Viral Response at 12 weeks: • L/S+Rx12: 100% • GS9669/S+Rx12: 92% • L/S+Rx6: 68% • L/Sx12: 70%	The most common reported adverse events: headache, fatigue, nausea

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Lawitz et al, 2013; PROTON[12] Phase II, multi-center, randomized trial	125	Treatment Naïve patients with Hepatitis C genotype 1, 2, or 3	Sofosbuvir (200 mg or 400 mg, x 12 weeks) + Interferon + Ribavirin (x 24-48 weeks; S + I/R) Placebo (x 12 weeks) + Interferon + Ribavirin (x 24-48 weeks; I/R)	Sustained Viral Response • S + I/R: 90-91% • I/R: 58%	Treatment-related discontinuation rate: • Sofosbuvir 200 mg: 2 (4%) • Sofosbuvir 400 mg: 3 (6%) • Placebo: 3 (12%) Most common adverse events: fatigue, headache, nausea, and chills
Kowdley et al, 2013; ATOMIC[35] Phase II, open-label, multi-center, randomized trial	332	Treatment Naïve patients with Hepatitis C genotype 1, 4, 5 or 6	Sofosbuvir + Interferon + Ribavirin (x 12 weeks) Sofosbuvir + Interferon + Ribavirin (x 24 weeks) Sofosbuvir + Interferon + Ribavirin (x 12 weeks) + Sofosbuvir (x 12 additional weeks) Sofosbuvir + Interferon + Ribavirin (x 12 weeks) + Sofosbuvir&Ribavirin (x 12 additional weeks)	Sustained Viral Response • All treatment durations: 82-100% • Genotype 1: 87-89% • Genotype 4: 82% • Genotype 6: 100%	Treatment-related adverse events: anemia and neutropenia
Lawitz et al, 2013; NEUTRINO[36] Phase III, open-label trial	327	Treatment Naïve patients with Hepatitis C genotype 1, 4, 5 or 6	Sofosbuvir + Interferon + Ribavirin (x 12 weeks; S + I/R) No comparator	Sustained Viral Response • S + I/R: 90%	Most common adverse events: fatigue, headache, nausea, and insomnia

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Lawitz et al, 2013; FISSION[36] Phase III, non-inferiority, randomized trial	499	Treatment Naïve patients with Hepatitis C genotype 2 or 3	Sofosbuvir + Ribavirin (S + R) Interferon + Ribavirin (I/R) Duration: 12 weeks	Sustained Viral Response S + R: • Genotype 2: 97% • Genotype 3: 56% I/R: • Genotype 2: 78% • Genotype 3: 63%	Influenza-like symptoms: • S + R: 3% • I/R: 16% Fever: • S + R: 3% • I/R: 18% Depression: • S + R: 5% • I/R: 14% Hematologic events: I/R > S + R
Jacobson et al, 2013; POSITRON[37] Phase III, double-blind, multi-center, randomized trial	278	Patients with Hepatitis C genotype 2 or 3 who are unsuitable to receive interferon	Sofosbuvir + Ribavirin (S + R) Ribavirin + Placebo (R) Duration: 12 weeks	Sustained Viral Response • S + R: 78% Genotype 2: 93% Genotype 3: 61% • R: 0%; $p < 0.001$	Serious adverse event rate: • S + R: 5% • R: 3% Fatigue S + R > R Insomnia S + R > R Anemia S + R > R
Jacobson et al, 2013; FUSION[37] Phase III, double-blind, multi-center, randomized trial	201	Patients with Hepatitis C genotype 2 or 3 who did not respond to initial treatment	Sofosbuvir + Ribavirin (x 12 weeks; S + R) Sofosbuvir + Ribavirin (x 16 weeks; S + R)	Sustained Viral Response S + R: • 12 weeks: 50% • 16 weeks: 73%; $p < 0.001$ • Genotype 2: 86-94% • Genotype 3: 30-62%	Serious adverse event rate: • 12 week: 5% • 16 week: 3%

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Zeuzum et al, 2014; VALENCE[38] Phase III, multi-center, randomized trial	419	Patients with Hepatitis C genotype 2 or 3	Sofosbuvir + Ribavirin (S + R) Placebo Duration: genotype 2- 12 weeks, genotype 3- 24 weeks	Sustained Viral Response S + R: • Genotype 2: 93% • Genotype 3: 85% • Placebo: 0%	Most common adverse events: headache, fatigue, and pruritus.
Osinusi et al, 2013; SPARE[34] Phase II, open-label, randimzed (weight-based or low-dose) trial	60	Treatment Naïve patients with Hepatitis C genotype 1	Sofosbuvir + low-dose Ribavirin (x 24 weeks; S + $_{ld}$R) Sofosbuvir + weight-based Ribavirin (x 24 weeks; S + $_{wb}$R)	Sustained Viral Response • S + $_{ld}$R: 68% • S + $_{wb}$R: 48%; p = NS	Most common adverse events: headache, anemia, fatigue, and nausea.
Lawitz et al, 2013; COSMOS[39] Phase II, randomized trial	186	Patients who may or may not have received previous treatment with Hepatitis C genotype 1	Sofosbuvir + Simeprevir + Ribavirin (x 12-24 weeks; S + S + R) Sofosbuvir + Simeprevir (x 12-24 weeks; S + S)	Sustained Viral Response (pooled analysis): 92%	Most common adverse events (pooled analysis): Fatigue: 52 (31%) Headache: 33 (20%) Nausea: 26 (16%)
Gane et al, 2013; ELECTRON[40] Phase II, open-label, randomized trial	95	Patient Naïve patients with Hepatitis C genotype 2 or 3	Sofosbuvir + Interferon + Ribavirin (S + I + R) Sofosbuvir + Ribavirin (S + S) Sofosbuvir monotherapy (S) Duration: 12 weeks	Sustained Viral Response at 24 weeks • S + I + R: 100% • S + R: 100% • S: 60%	Most common adverse events: headache, fatigue, insomnia, nausea, rash, and anemia.

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Molina et al, 2015; PHOTON-2[41] Open-label, non-randomised, uncontrolled, multi-center (45 sites in 7 European countries and Australia), phase 3 study	275	Patients (aged ≥18 years) co-infected with stable human immunodeficiency virus (HIV) and hepatitis C virus (HCV) genotypes 1-4	Sofosbuvir 400 mg once daily plus ribavirin (1000 mg in patients <75 kg or 1200 mg in patients ≥75 kg) twice daily Duration: 12 weeks in treatment-naive patients with genotype-2 OR 24 weeks in all other patients; February 7, 2013 to July 29, 2013	Sustained Viral Response at 12 weeks: Genotype-1: 85% (95% CI 77-91) Genotype-2: 88% (69-98) Genotype-3: 89% (81-94) Genotype-4: 84% (66-95) Overall Response Rates: Treatment-naive patients with HCV genotypes 2 or 3: 89% [95% CI 67-99] and 91% [81-97] Treatment-experienced patients with HCV genotypes 2 or 3: 83% [36-100] and 86% [73-94]	Treatment-related discontinuation rate: 2% (6/275) The most common adverse events: fatigue, insomnia, asthenia, headache.

Evidence Table 2. Clinical Trials Evaluating Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Sulkowski et al, 2015; TURQUOISE-I[29] Randomized, multi-center (17 sites in the United States and Puerto Rico), open-label study	63	Patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) at high risk for liver disease progression who were HCV treatment-naive or had history of prior treatment failure with peginterferon plus ribavirin therapy.	Ombitasvir, paritaprevir, ritonavir dasabuvir and ribavirin Duration: 12-24 weeks; September 2013 and August 2014	Sustained Viral Response at 12 weeks: 29/31 (94%; 95% CI, 79%-98%) Sustained Viral Response at 24 weeks: 29/32 patients (91%; 95% CI, 76%-97%) *Of the 5 patients who did not achieve SVR: • 1 withdrew consent • 2 confirmed virologic relapse or breakthrough • 2 had clinical history and phylogenetic evidence consistent with HCV reinfection	The most common treatment-emergent adverse events: fatigue (48%), insomnia (19%), nausea (18%), headache (16%)
Kwo et al, 2014[30] Phase 2, open-label, multi-center trial	34	Liver-transplant recipients with no fibrosis or mild fibrosis	Ombitasvir (25 mg), paritaprevir (150 mg), ritonavir (100 mg), dasabuvir (250 mg) and ribavirin Duration: 24 weeks	Sustained Viral Response at 24 weeks: 33/34 (97%, 95% CI 85-100)	The most common adverse events: fatigue, headache, cough Required erythropoietin: 5 (15%) Discontinuation rate: 1 (3%)

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Andreone et al, 2014[25] Multicenter, open-label, phase 3 trial	179	Patients with HCV genotype 1b infection, without cirrhosis, previously treated with peginterferon and ribavirin	Ombitasvir, paritaprevir, ritonavir and dasabuvir with ribavirin (V+R) Ombitasvir, paritaprevir, ritonavir and dasabuvir without ribavirin (V-R) Historical comparator: Telaprevir, peginterferon and ribavirin (TPR) Duration: 12 weeks	Sustained Viral Response at 12 weeks: • V+R: 96.6% • V-R: 100% TPR: 64%	The most common adverse events: Fatigue • V+R: 31.9% • V-R: 15.8% Headache • V+R: 24.2% • V-R: 23.2% Decreases in hemoglobin level: • V+R: 42% V-R: 5.5%; $p < 0.001$
Ferenci et al, 2014; PEARL III/IV[23] Two randomized, controlled, phase 3 trials	724	Previously untreated patients with HCV genotype 1b infection (419) or genotype 1a infection (305) who did not have cirrhosis	Ombitasvir, paritaprevir, ritonavir and dasabuvir with ribavirin (V+R) Ombitasvir, paritaprevir, ritonavir and dasabuvir without ribavirin (V-R) Duration: 12 weeks	Sustained Viral Response at 12 weeks: • V+R: 97.5-99% • V-R: 90.2-99% •	Overall adverse event rate: • V+R: 80-92% • V-R: 67-82%; $p \leq 0.03$ Decreases in hemoglobin level: • V+R: 42-51% • V-R: 3.4-3.9%; $p \leq 0.003$ The most common adverse events: fatigue, headache, nausea
Poordad et al, 2014[27] Open-label phase 3 trial	380	Previously untreated and previously treated adults with HCV genotype 1 infection and compensated cirrhosis	Ombitasvir, paritaprevir, ritonavir and dasabuvir with ribavirin Duration: 12-24 weeks	Sustained Viral Response: • 12 weeks: 91.8% (191/208) • 24 weeks: 95.9% (165/172)	The most common adverse events: Fatigue • 12 weeks: 32.7% • 24 weeks: 46.5% Headache • 12 weeks: 27.9% • 24 weeks: 30.8% Nausea • 12 weeks: 17.8% 24 weeks: 20.3%

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Feld et al, 2014[24] Multicenter, randomized, double-blind, placebo-controlled trial	631	Previously untreated patients with HCV genotype 1 infection	Ombitasvir, paritaprevir, ritonavir and dasabuvir with ribavirin Placebo Historical comparator: Telaprevir with peginterferon and ribavirin Duration: 12 weeks	• Sustained Viral Response at 12 weeks: 96.2% (95% CI, 94.5-97.9)	Overall Adverse event rate: • Active: 87.5% • Placebo: 73.4%; p < 0.001 The most common adverse events nausea, pruritus, insomnia, diarrhea, asthenia: active > placebo; p < 0.05 Reduced hemoglobin levels: • Active: 5.8-47.5% Placebo: 2.5%
Zeuzem et al, 2014[26] Randomized, double-blind, placebo-controlled, phase 3 trial	394	Patients with HCV genotype 1 infection and no cirrhosis previously treated with peginterferon-ribavirin	Ombitasvir, paritaprevir, ritonavir and dasabuvir with ribavirin Placebo Historical comparator: Telaprevir with peginterferon and ribavirin Duration: 12 weeks	• Sustained Viral Response at 12 weeks: 96.3% (95% CI, 94.2 to 98.4)	Pruritus • Active: 13.8% • Placebo: 5.2%; p = 0.03 Discontinuation Rate: • Active: 1% • Placebo: 0% Reduced hemoglobin levels: • Active: 0.3-4.7% Placebo: 0%

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Kowdley et al, 2014[28] Phase 2b, open-label study with 14 treatment subgroups	571	Patients with HCV genotype 1 infection without cirrhosis who had not received treatment previously or who had not had a response to prior therapy	Ombitasvir, paritaprevir, ritonavir and dasabuvir with ribavirin (V+R) Ombitasvir, paritaprevir, ritonavir with ribavirin Dasabuvir, paritaprevir, ritonavir with ribavirin Duration: 8, 12, or 24 weeks	Sustained Viral Response at 12 weeks Across all treatment groups: 83-100% V+R: 8 weeks - 88% • 12 weeks - 95%	• The most frequent adverse events: fatigue, headache, nausea, insomnia

Key: Vedroprevir = GS-9451